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GUIDELINES

RSSDI Clinical Practice Recommendations for Management of Type 2 Diabetes Mellitus, 2015

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Abbreviations (alphabetical order)

AGIs alpha-glucosidase inhibitors

ADA american diabetes association

BMI dody mass index

CVD cardiovascular disease

CURES chennai urban rural epidemiological study

CKD chronic kidney disease

CAD coronary artery disease

DM diabetes mellitus

DSME diabetes self-management education

DKD diabetic kidney disease

DPN diabetic nephropathy

DN diabetic neuropathy

NSS neuropathy symptom score

DR diabetic retinopathy

DPP-4 dipeptidyl peptidase-4

ESRD end stage renal disease

FPG fasting plasma glucose

GPs general practitioners

GLP-1 glucagon like peptide-1

GI glycemic index

HbA1c glycated hemoglobin

HDL high density lipoprotein

IFG impaired fasting glucose

IGT impaired glucose tolerance

IDRS indian diabetes risk score

IR insulin resistance

IDF international diabetes federation

MNT medical nutrition therapy

MS metabolic syndrome

MUFA monounsaturated fatty acids

NDS neuropathy disability score

NGT normal glucose tolerance

OR odds ratio

OADs oral antidiabetic agents

OGTT oral glucose tolerance test

PUFA polyunsaturated fatty acids

PPG post prandial glucose

PPHG post-meal hyperglycemia

SMBG self-monitoring of blood glucose

SGLT 2 sodium-glucose cotransporter 2

SU sulfonylurea

TZD thiazolidinedione

T2DM type 2 diabetes mellitus

WC waist circumference

WHR waist to hip ratio

WHO world health organization

Preface

Good glycemic control is the cornerstone for management of diabetes. Despite availability of extensive evidence on optimal management of diabetes, an alarming increase in its prevalence is observed worldwide [1]. According to the International Diabetes Federation (IDF), there are approximately 382 million people with diabetes in 2014, and this number is expected to reach 592 million by 2035 [1]. The regional prevalence of diabetes among adults of South East Asia was estimated at 8.2% (72 million) in 2013, which is projected to increase to 10.1% (123 million) in 2035 [2]. Diabetes has emerged as one of the major public health concern in Asian countries which harbor more than 60% of the world's diabetic population. It is estimated that, for every diagnosed case of diabetes in Asia, there is at least one undiagnosed case of glucose intolerance, suggesting that the actual population at risk would be much higher than the actual estimates. The epidemic of diabetes in India is at its worst with as many as 66.85 million diabetes patients in 2014 of which 35.5 million are undiagnosed cases of diabetes in 2014 [1]. These numbers are based on the ICMR-INDIAB National Study which reported that 62.4 million people had diabetes in 2011 and 77 million had pre-diabetes [3]. It is predicted that by 2035 diabetes may afflict up to 109 million persons in India, being rightly referred to as "diabetes capital of the world" [1]. Numerous factors including demographic, lifestyle (physical activity, diet), genetic, socio-economic (urbanization, education, income), cultural and psychological (stress) we know and understand and which we do not know can influence the prevalence of obesity and diabetes [4]. Considering the current demographic pattern with 46% people with 0-19 years of age and high prevalence of obesity in adolescence, a second surge of increase in prevalence is anticipated after 3-4 decades. However, it may be conceptualized that adoption of sound methods of increasing awareness though diabetes education, behavioral changes and promotion of healthy lifestyle together with continuous efforts to screen for diabetes and healthy town planning may blunt the slope of the diabetes curve and curb the second epidemic of diabetes that is likely after 2–3 decades [5].

Type 2 diabetes mellitus (T2DM) is often asymptomatic in its early stages and can remain undiagnosed for many years. During this period the body is exposed to excess blood glucose (hyperglycemia) resulting in irreversible organ damage. By the time T2DM is diagnosed, many of the complications of T2DM have already developed in these patients. In Asian Indians, T2DM occurs almost a decade earlier than the Caucasians [3]. They have greater predilection for cardiovascular (CV) complications such as coronary artery disease (CAD) and atherosclerosis at any age point [6, 7], and have significant procoagulant tendencies [8-10]. Many Asian Indians develop metabolic syndrome and diabetes at body mass index (BMI) <25 kg/m^2, which is generally considered normal among whites. In spite of a relatively lower rate of obesity as defined by BMI cut off points, Indians tend to have larger waist circumference (WC) and waist-to-hip ratios, indicating a greater degree of central body obesity [11]. This is often associated with a characteristic metabolic profile with higher insulin levels [12] and greater degree of insulin resistance (IR) [13, 14] and therefore hyperinsulinemia is a common feature even in normoglycemic non-obese subjects [15]. These unique clinical and biochemical characteristics that are commonly found among Asian Indians are collectively referred to as the "Asian Indian Phenotype" or thin-fat phenotype representing metabolically obese, normal weight individuals [16,17]. This also explains why BMI may underestimate the cardio metabolic risk which may be best evaluated by WC or waist-hip ratio [18-20].

Phenotypic differences in obesity and body composition between South Asians and Caucasians are in part responsible for greater metabolic perturbations in the former and have great implications for pathophysiology, management and prevention of obesity–related diseases [19,21,22]. Evidence from prospective studies suggests that Asian Indians have higher levels of fasting insulin compared to Caucasians. Fasting insulin levels have been found to be a surrogate marker of IR and a predictor of CAD. Most of the CV risk factors like dyslipidemia, hypertension, obesity, central obesity, and glucose intolerance have been shown to be associated with IR, and a combination of these abnormalities could lead to CAD [23,24]. The presence of a high genetic predisposition to diabetes, prevalence of IR syndrome and the consequences of modernization leading to life style changes, make an Asian Indian highly susceptible to developing diabetes at a young age [25]. In addition, Asian Indians with mild dysglycemia were found to have beta-cell dysfunction [26] and higher HOMA-IR that were associated with deterioration of glycemia. However, beta-cell dysfunction appears to occur early in the natural history of T2DM, and this may be a key factor in pathogenesis of the disorder in Asian Indians [27]. All these factors concerning Indians underscores the need to consider the Indian diabetic patient as unique, requiring management approaches tailored to suit these specific needs.

National guidelines and standards of care for diabetes are now available in many countries in the world. Their experience has shown that adopting guidelines by the clinicians improves the outcome of treatment. Considering the need of a standard diabetes care, Ministry of Health and Family welfare, Government of India launched the National Programme on Prevention and Control of Diabetes, Cardiovascular diseases and Stroke (NPDCS) in 2008. In addition, several organizations including ICMR published Indian specific diabetes care guidelines. Despite these efforts diabetes management practices in India remain less than satisfactory. This is partly due to diverse religions, cultures, languages, food habits, lifestyles,

and traditions that impact management practices for diabetes. The high burden of diabetes in India is mostly borne by general physicians and primary care practitioners who often find it difficult when selecting optimal treatment strategies, especially when prognosis remains unpredictable in spite of aggressive management. The phenomenon of deteriorating glycemic status, attributed to the natural course of the disease and lack of stringent measures to eradicate root cause of the disease presents physicians with unique challenges in managing their patients with diabetes. The increasing complexity of evidence base and diabetes care in itself perplexes both patient and physicians about the standard of care to be followed to curtail the progression of diabetes. Moreover, diabetes care is further hampered by increasing prevalence of diabetes related micro and macro-vascular complications and associated disorders (hypertension, obesity, metabolic syndrome and dyslipidemia), complicating the management aspects.

The lack of uniformity and standardization prevailing in current guidelines and protocols for health care providers, including standards for health-care facilities, personnel and treatment protocols, makes it difficult to monitor and assure quality services across the board. Hence, a need for county-specific harmonized form of these guidelines addressing the needs of Indian patients with diabetes was observed. The current document developed by Research Society for the Study of Diabetes in India is a derived guideline, adapted from IDF Guidelines 2014. In addition to defining standard care for diabetes, the guideline also considers the economic realities of our people, making it more affordable for the average Indian. It is expected that these recommendations will help define practically implementable best practices not only for management of T2DM but also prevention of acute and chronic complications of diabetes by primary care physicians across India. This practical approach facilitates implementation of cost-effective evidence-based diabetes care to be followed and adhered to by all the health care professionals including practicing physicians, and specialists in limited resource settings like India.

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Methodology

In view of the current status of diabetes in India, a steering committee of RSSDI involving experienced diabetologists and endocrinologists across India was constituted which met twice in the year 2015 and discussed the adaptability and implementation of the IDF clinical practice guidelines for management of T2DM in India. This was done keeping in view various economic and sociocultural constraints, resource constraints in our country including human resource as well as constraints of access to healthcare. Therefore the current guideline should be considered as 'derived guideline', developed from the source IDF 2014 'Global Guidelines for Type 2 Diabetes'. This guideline presents the deliberations of the group who facilitated the discussion and contributed to the development of this document. Considering that the implementation of particular standards of care is limited by lack of resources, only "Recommended care" and "Limited care" setting of the IDF guidelines have been considered while the "Comprehensive care" was omitted. This practical approach facilitates implementation of cost-effective evidence-based care in limited resource settings like India.

- *Recommended care* constitutes evidence-based care which is cost-effective interventions that should be made available to all people with diabetes with an aim of any health-care system to achieve this level of care.
- *Limited care* is the lowest level of care that seeks to achieve the major objectives of diabetes management provided in health-care settings with very limited resources – drugs, personnel, technologies and procedures.

The steering committee deliberated, defined the scope, remitted the guidelines and decided that these would be national guidelines for the management of T2DM, covering all ages of patients with diabetes and would be developed for the primary care physician and specialist. The specific areas on which recommendations needed to be developed were also finalized. Expert panel groups were constituted including one or more steering committee members as coordinators and 3-5 or more national experts to review all available Indian evidence and Asian/global evidence wherever required in their area and make suitable recommendations.

The members of the expert panel examined the IDF recommendations and formulated recommendations based on current disease concepts among physicians, available research evidence, and economic and logistic constraints prevalent in India. For topics with no IDF specific guidelines, other relevant guidelines were considered or the group conducted a systematic review of medical literature to provide the best possible evidence base. Where there was little or no evidence, the group relied on their clinical experience and expertise, judgment and consensus to make the recommendations. There was a broad agreement on most of the recommendations made by the IDF workgroup. However, the RSSDI expert panel members commented on specific areas and amplified certain concepts where it was felt that further guidance that goes beyond what is stated in the IDF guidelines might help

the primary care practitioners and physicians in India in their appropriate implementation.

The decision on the analytical re-evaluation of the recommendations proposed by IDF workgroup, was based on the Indian evidence published between 1990 and 2015, and following a review of relevant local factors in Indian context. This included Indian evidence from Indexed literature searches, articles published in International Journal of Diabetes in Developing countries (IJDDC), RSSDI textbook of Diabetes (3rd edition) [1,2], Journal of Association of Physicians of India (JAPI) and personal communications from authors. Where Indian evidence was not available Asian evidence was considered if available.

Various factors of relevance to the Indian context that were considered by different expert panel groups and reviewed by the steering group were:

- High prevalence of prediabetes and diabetes
- Onset of T2DM at least a decade earlier that in western countries
- High prevalence of diabetes-related micro and macro vascular complications
- Large rural-urban divide
- Cost of diagnosis, treatment, monitoring and prevention
- Sedentary lifestyles/physical inactivity
- Limited resources
- Poverty and illiteracy
- Psychosocial and cultural factors
- Adherence and compliance to anti-diabetic therapy

The recommendations of the expert panel groups were reviewed by the steering committee and were then finalized by the writing group as a draft consensus document. The draft consensus document was sent out for wide consultation to the national and regional members of all RSSDI chapters, all key opinion leaders in the country, representatives of other Diabetes and Physician organizations in India, interested industry and academic professionals and to a large section of physicians, diabetologists and endocrinologists in the country. The same was also put up on the society website for any suggestions. The suggestions/comments provided by them were reviewed by the steering committee and the draft was accordingly updated, where appropriate.

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Diagnosis of diabetes

RSSDI 2015 recommendations

Recommended care

Diabetes can be diagnosed on any of the following criteria:

- Fasting plasma glucose (FPG) ≥ 126mg/dL**or*
- Oral glucose tolerance test (OGTT) using 75 gms of anhydrous glucose with FPG ≥ 126 mg/dl and/or 2 hour plasma glucose ≥ 200 mg/dL *or*
- Glycated hemoglobin (HbA1c) ≥ 6.5% ***or*
- Random plasma glucose ≥ 200 mg/dl in the presence of classical diabetes symptoms
- Asymptomatic individuals with a single abnormal test should have the test repeated to confirm the diagnosis unless the result is unequivocally abnormal.

Limited care

- FPG ≥126mg/dL**or*
- 75 g OGTT (using 75 gms of anhydrous glucose) with FPG ≥ 126 mg/dL and/or
  2 hour plasma glucose ≥ 200 mg/dL *or*
- Random plasma glucose ≥ 200 mg/dL in the presence of classical diabetes symptoms
- Asymptomatic individuals with a single abnormal test should have the test repeated to confirm the diagnosis unless the result is unequivocally abnormal.

**FPG is defined as glucose estimated after no caloric intake for at least 8-12 hours.*

*** Using a method that is National Glycohemoglobin Standardization Programme (NGSP) certified. For more on HbA1c & NGSP, please visit http://www.ngsp.org/index.asp*

NOTE:

1. Point of care device for estimation of HbA1c is not recommended for diagnosis
2. Capillary glucose estimation methods are not recommended for diagnosis
3. Venous Plasma is used for estimation of Blood glucose
   a. Plasma must be separated soon after collection because the blood glucose levels drop by 5-8% hourly if whole blood is stored at room temperature.

For more details on glucose estimation visit: http://www.ncbi.nlm.nih.gov/books/NBK248/

Preamble

Traditionally measuring FPG and OGTT is often considered for diagnosis [1], despite several international guidelines recommending HbA1c as a diagnostic tool for detecting diabetes/prediabetes [2,3]. The optimal cut-off value of HbA1c to diagnose diabetes is determined in a way that individuals with HbA1c levels above a certain cut-off value have a much larger probability of having or developing a diabetes-related complication [4]. However in several countries including India, there is no consensus on a suitable cut-off point of HbA1c for diagnosis of diabetes. Moreover measuring HbA1c is more expensive than FPG [5] and standardization of measurement techniques is poor across the country. In lieu of this, the panel felt that using HbA1c as a sole criteria for diagnosis of diabetes is inappropriate in resource constraint settings and framing guidelines based on fasting or 2-hour plasma glucose or OGTT to detect or diagnose diabetes would be more appropriate in limited resource settings like India.

Considerations

The decision about setting diagnostic thresholds values was based on the cost effective strategies for diagnosing diabetes that were reviewed in Indian context.

Rationale and evidence

HbA1c cut off for diagnosis for Indian patients

- The panel opined that HbA1c cut off point of 6.5% is optimal for diagnosis of diabetes in Indian patients. This was based on the data available from 3 centers in India: Chandigarh, Chennai and Bangalore. Data from a community based randomized cross sectional study in urban Chandigarh suggested that HbA1c cut point of 6.5% has optimal specificity of 88%, while cut off point of 7.0% had sensitivity of 92% for diagnosis of diabetes [6]. On the other hand, data from Chennai Urban Rural Epidemiology Study demonstrated 88.0% sensitivity and 87.9% specificity for detection of diabetes when HbA1c cut off point was 6.1% (based on 2-hour post load plasma glucose) and 93.3% sensitivity and 92.3% specificity when HbA1c cut off point was 6.4% (when diabetes was defined as FPG > or =7.0 mmol/l) [7]. Similarly, Bangalore study suggests that diagnosis of diabetes based on HbA1c of 6.5% would be more precise as it is expected to be more sensitive [8].
- The panel opined that HbA1c cannot be used as 'sole' measurement for diagnosis of diabetes in Indian settings. However, panel emphasized that HbA1c can be used in settings where an appropriate standardized method is available.

Implementation

Individuals should be educated on the advantages of early diagnosis and should be encouraged to participate in community screening programs for diagnosis.

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Screening/early detection of diabetes/prediabetes

RSSDI 2015 recommendations

Screening/early detection of diabetes

Recommended care

- Each health service should decide whether to have a program to detect people with undiagnosed diabetes
  - This decision should be based on the prevalence of undiagnosed diabetes and available support from health-care system/service capable of effectively treating newly detected cases of diabetes
  - Opportunistic screening for undiagnosed diabetes and prediabetes is recommended. These should include:
    - Individuals presenting to health care settings for unrelated illness
    - Family members of diabetic patients
    - Antenatal care
    - People over the age of 30 years should be encouraged for voluntary testing for diabetes)
  - Community screening may be done wherever feasible
- Detection programs should be usually based on a two-step approach:
  - Step 1 - Identify high-risk individuals using a risk assessment questionnaire Indian Diabetes Risk Score (IDRS) is recommended for Indians.
  - Step 2 - Glycemic measure in high-risk individuals.
- Where a random non-FPG level ≥100 mg/dL to 200 mg/dL is detected, FPG should be measured, or OGTT should be performed
- Use of HbA1c as a sole diagnostic test for screening for diabetes/prediabetes is not recommended
- People with screen-positive diabetes need diagnostic testing to confirm diagnosis while those with screen-negative to diabetes should be re-tested after 3 years
- Paramedical personnel such as nurses or other trained workers be included as a part of any basic diabetes care team

Limited care

- Detection programs should be opportunistic and limited to high-risk individuals in very limited settings
- The principles for screening are as for *Recommended* care
- Diagnosis should be based on FPG or capillary plasma glucose if only point-of-care testing is available
- Using FPG alone for diagnosis has limitations as it is less sensitive than 2-hour plasma glucose in Indians to diagnose diabetes

Prediabetes

Recommended care

- People with screen-positive for prediabetes (FPG:100 mg/dL to 125 mg/dL or 2-hour plasma glucose in the 75-g OGTT: 140 mg/dL to 199 mg/dL or HbA1c: 5.7% to 6.4%) should be monitored for development of diabetes annually and simultaneously screened and treated for modifiable risk factors for cardiovascular disease such as hypertension, dyslipidemia, smoking and alcohol consumption
- Screening strategies should be linked to healthcare system with capacity to provide advice on lifestyle modifications:
  - Screening strategies should be aligned with on-going support national programs available at community health centers or above
  - Patients with impaired glucose tolerance (IGT), impaired fasting glucose (IFG) should be referred to these ongoing support programs
- People with prediabetes should modify their lifestyle including:
  - Attempts to lose 5 to 10% of body weight if overweight or obese
  - Participate in moderate physical activity (e.g. walking) for at least 150 mins/week
  - 6-8 hours of sleep daily
- Healthy lifestyle measures including diet and physical activity are equally important for non-obese patients with T2DM also
- People with prediabetes failing to achieve any benefit on lifestyle modifications after 6 months, should be initiated on oral antidiabetic agents
  - Metformin: In younger individuals with one or more additional risk factors for diabetes regardless of body mass index
  - Alternatively alpha glucosidase inhibitors such as acarbose or voglibose may be initiated if metformin is not tolerated.

- Other pharmacological interventions with pioglitazones, orlistat, vitamin D or bariatric surgery are not recommended
- People with prediabetes should be educated on
  - weight management
  - physical activity
  - alcohol and tobacco consumption

Limited care

- The principles of detection and management of prediabetes are same as for Recommended care
- Linkages to healthcare system with capacity to provide advice on lifestyle modifications and alignment with ongoing support national programs available at community health centers where patients detected with prediabetes can be referred are critical

Preamble

Chronic hyperglycemia is associated with significantly higher risk of developing diabetes related microvascular and macro vascular complications. Early detection of diabetes/pre-diabetes through screening increases the likelihood of identifying asymptomatic individuals and receives adequate treatment to reduce the burden of diabetes and its complications. Adopting a targeted approach and utilizing low-cost tools with meticulous planning and judicious allocation of resources can make screening cost-effective even in resource-constrained settings like India [1].

Prediabetes is defined by blood glucose concentrations higher than normal, but lower than established thresholds for diagnosis of diabetes. People with prediabetes are defined by having IGT (2-hour plasma glucose in the 75-g OGTT: 140 mg/dL to 199 mg/dL) or IFG (FPG: 100 mg/dL to 125 mg/dL). It is a state of intermediate hyperglycemia with increased risk of developing diabetes and associated cardiovascular complications and therefore early detection and treatment of prediabetic IGT and IFG is necessary to prevent the rising epidemic of diabetes and its associated morbidity and mortality. Although, IDF guideline does not deal with screening and management of prediabetes, given high prevalence rates of prediabetes in our country, it was felt by the RSSDI panel members that including screening and management aspects of prediabetes is logical and will provide an important opportunity for prevention of diabetes in India.

Considerations

The decision about conducting a screening program should be based on the following local factors that were reviewed in Indian context which include: limited resources, lack of quality assurance in labs, high risk population for diabetes, large unrecognized burden of undiagnosed diabetes, high prevalence of prediabetes, among fastest converting population form prediabetes to diabetes, large Rural–Urban divide, largely sedentary population in Urban areas, onset of T2DM at least a decade earlier that in western countries, newer technologies for screening, cost of early detection to the individual, capacity for carrying out screening and capacity to treat/manage screen positive individuals with diabetes and prediabetes.

Rationale

Opportunistic screening

- The panel opined that screening should be opportunistic but not community based as they are less effective outside healthcare setting and poorly targeted i.e. it may fail to identify individuals who are at risk [2]. Opportunistic screening is more cost-effective with better feasibility within the healthcare system while minimizing the danger of medicalizing a situation. However, community screening may be carried out wherever feasible.
- The panel suggested opportunistic screening in
  - Individuals presenting to health care settings for unrelated illness
  - Adult family members of diabetic patients
  - Antenatal care
  - People over the age of 30 years should be encouraged for voluntary testing for diabetes.

Risk assessment questionnaire

- The panel suggested the use of simple and validated risk assessment questionnaires such as IDRS for detecting undiagnosed prediabetes and diabetes (Annexure I). It is recommended that IDRS be used for this purpose in our country. This simplified IDRS toll was found to be useful for identifying undiagnosed subjects with diabetes in India and could make screening programs more cost effective [3]. This is the best available and most validated risk score and which is also used in several national programs for prevention of not only diabetes but also cardio metabolic disease such as stroke. Also its applicability in identifying prevalence of diabetes-related complications such as CAD, peripheral vascular disease and neuropathy among T2DM patients was found to be successful [4].

Random plasma glucose level

- The panel endorsed the IDF recommendation on the need to measure FPG and perform OGTT based on random plasma glucose levels which were associated with the development of diabetes (2HrPG of ≥200 mg/dL) or prediabetes (2HrPG of ≥140 to <200 mg/dL) [5]. According to IDF guidelines, FPG values ≤100 mg/dL are considered normal. Anything above 100 mg/dL were considered to be at risk of developing diabetes. Moreover, people with a FPG levels between 100 to 125 mg/dL have IFG suggesting that person with IFG is at an increased risk of developing T2DM. A level of 126 mg/dL or above, confirmed by repeating the test on another day, means a person has diabetes [6].
- The panel opined that although the present criteria of IFG (100 mg/dL to 125 mg/dL) may be sensitive and have lesser variability, measuring 2 hour plasma glucose levels may give more accuracy and confidence in targeting this population for prevention strategies.

HbA1c as criteria for screening

- The panel opined that use of HbA1c as sole criteria for screening for diabetes/prediabetes would be inappropriate in most settings in our country at this time. However HbA1c may be utilized for screening if it is being done from a lab known to be well equipped with external quality assurance.
- The panel also cautioned on the concerns of high prevalence of anaemia and high prevalence of hemoglobinopathies in certain regions/populations particularly from the North East as these can have significant impact when HbA1c is used as diagnostics test for screening.

Diagnosis of prediabetes

- The panel endorsed the American Diabetes Association (ADA) criteria for diagnosis of prediabetes for Indian context

Glycemic parameter	Values
Fasting plasma glucose	100 mg/dL to 125 mg/dL
2-hour plasma glucose in the 75-g OGTT	140 mg/dL to 199 mg/dL
HbA1c	5.7% to 6.4%

Re-screening

- The panel emphasized on striking balance between cost of screening and cost of treating complications.
- On the basis of expert opinion of the panel, the general population should be evaluated for the risk of diabetes by their health care provider on annual basis beginning at age 30.
- Yearly or more frequent testing should be considered in individuals if the initial screen test results are in the prediabetes range or present with one or more risk factors that may predispose to development of diabetes.
- The panel opined that screening programs should be linked with healthcare system and on-going national prevention programs that will facilitate effective and easy identification of people at high risk of developing diabetes and its complications.

Paramedical personnel

- Paramedical personnel can play a key role as facilitator in imparting basic self-management skills to diabetic patients and those at risk for diabetes. They can be actively involved in engaging people with diabetes or at risk of diabetes in implementing diet and lifestyle changes, behavioral changes, weight management, pre pregnancy counselling and other preventive education.
- Nurses or other trained workers in primary care settings and in hospital outpatient settings can:
  - Help in Identification of people at risk for diabetes
  - Help in recognition of symptoms of diabetes, hypoglycemia and ketosis
  - Help in timely referral of these cases
  - Nurses or Nurse Educators in secondary and tertiary care settings can:
  - Perform all the above activities
  - Help in prevention and treatment of hypoglycemia
  - Help in problems with insulin use

Evidence

It has been observed that Indians are more prone to diabetes at younger age and at lower BMI compared to their Western counterparts [7]. The reason for this difference has been attributed to "Asian Indian phenotype" characterized by low BMI, higher body fat, visceral fat and WC, lower skeletal muscle mass and profoundly higher rates of IR [8,9]. The 10-Year follow-up data of the Chennai Urban Rural Epidemiology Study (CURES) that assessed incident rates dysglycemia in Asian Indians are now

available [10]. According to researchers, the Asian Indians were found to have one of the highest incidence rates of diabetes (diabetes, prediabetes, and any dysglycemia: 22.2, 29.5, and 51.7 per 1,000 person-years, respectively), with rapid conversion from norm glycemia to dysglycemia (45.1%). Predictors of progression to dysglycemia were advancing age, family history of diabetes, 2-h plasma glucose, HbA1c, low high density lipoprotein (HDL) cholesterol, and physical inactivity. Despite the escalating burden, the current evidence on the prevention of T2DM and its complications in India still remain scanty. Though the general practitioners (GPs) in India are well aware of symptoms and complications of T2DM, they are oblivious regarding the use of standard screening tests resulting in significant delay in diagnosis and treatment [11]. Considering significant resource constraints together with awareness levels of patients and physicians, there is a need for prevention strategies that are culturally relevant and cost-effective [12]. Following section covers evidence from India studies on various strategies that were helpful in detecting and minimizing the risk of development of diabetes and its associated complications.

- Simplified tools for detection of diabetes such as IDRS tool was found to be useful for identifying undiagnosed subjects with diabetes in India and could make screening programs more cost effective [3]. In a recent survey that estimated the utility of Madras Diabetes Research Foundation-Indian Diabetes Risk Score (MDRF-IDRS) in identifying risk for diabetes mellitus in Indian adult population aged 30 years, found statistically significant association between IDRS and diabetes mellitus patients indicating MDRF-IDRS to be efficient tool to screen and diagnose the huge pool of undiagnosed diabetics in India [13].
- Other novel non-invasive screening tools such as EZSCAN [14], Pedobarography [15], Michigan Neuropathy Screening Instrument (MNSI), and Optimal Scaling Combination (OSC) [16] have also been evaluated in Asian population with T2DM. These tools were found to be of diagnostic significance for early detection of metabolic syndrome (MS), IGT and diabetes mellitus (DM), normal glucose tolerance (NGT) and related complications such as diabetic kidney disease (DKD) [16], diabetic foot problems [17] and diabetic peripheral neuropathy [15]. However there are a lot of false positive and false negative results with these non-invasive screening tools and currently the panel does not recommend using these tools for diagnosis of diabetes or pre-diabetes, in the absence of the gold standard tests based on blood glucose testing outlined above.
- The panel suggested that individuals with diabetes or at risk of developing diabetes should be advised on lifestyle changes and implementing strategies focusing on diet, exercise and weight loss to prevent the risk of progression and thus complications of diabetes [18].
- Evidence from literature suggests that initial lifestyle intervention are cost-effective [19] and can significantly reduce the incidence of diabetes in Asian Indians with IGT or with combined IGT + IFG [20,21]. In Patients in whom metformin is contraindicated, alpha glucosidase inhibitors such as acarbose or voglibose may be used, as they confer lesser side-effects compared to other oral antidiabetic agents. Furthermore, lifestyle intervention with diet and exercise in those with IGT can significantly decrease the incidence of diabetes and its complications [22,23] while providing long-term beneficial effects for up to 20 years [24].
- Optimal sleep (7–8 hours per night) has been shown to maintain metabolic health, aid in weight loss and increase insulin sensitivity while short-duration (<5-6 hrs.) or longer-duration (>8-9 hrs.) of sleep was associated with increased risk of diabetes [25,26].
- Interventions predominantly based on counselling and education were found to be effective in preventing/reducing the risk of developing diabetes and its complication and also helps in improving dietary patterns of individuals with pre-diabetes and diabetes [12,27]. Mobile phone messaging was found to be an inexpensive and most effective alternative way to deliver educational and motivational advice and support towards lifestyle modification in high risk individuals [28].
- Dietary interventions such as high-carbohydrate low-fat diet [29], fiber-rich [30] and protein-rich diet [31,32] have found to have definite role in prevention of diabetes.
- Evidence from the Chennai Urban Rural Epidemiology Study (CURES) and [PACE] Diabetes Project, suggests that awareness and knowledge regarding diabetes is inadequate among patients in India and implementation of educational programs at massive level can greatly improve the awareness on diabetes and its associated CVD [33,34]. Moreover, mass awareness and screening programs through community empowerment, were found to effectively prevent and control diabetes and its complications such as foot amputations [35].
- Currently the role of yoga and fenugreek in the prevention of diabetes is being evaluated in the Indian prevention of Diabetes Study by RSSDI.

Implementation

A clear and transparent decision should be made about whether or not to endorse a screening strategy. If the decision is in

favor of screening, this should be supported by local protocols and guidelines, and public and health-care professional education campaigns.

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Obesity and diabetes

RSSDI 2015 recommendations

Recommended care

- Maintaining healthy lifestyle is recommended for management of metabolic syndrome. This includes:
  - Moderate calorie restriction (to achieve a 5–10 per cent loss of body weight in the first year)
  - Moderate increase in physical activity
  - Change in dietary composition
- IDRS is a simple and cost effective tool for identifying obesity and lipid abnormalities in patients with T2DM and should be recommended in this patient population for identifying high risk individuals
- People with type 2 diabetes should be initiated on exercise therapy, prescribing a combination of aerobic and muscle strengthening activities
- Pharmacotherapy for obese type 2 diabetes patients should be considered in addition to lifestyle changes in those with BMI>27kg/m^2 without co-morbidity, or a BMI >25kg/m^2 with co-morbidity
  - Metformin should be first line drug for all type 2 diabetes patients
  - Lipase inhibitors (Orlistat)) may be used for inducing weight loss.
  - GLP-1 analogues (exenatide and liraglutide) and SGLT-2 inhibitors (Canagliflozin, Dapagliflozin) may be preferred as add-ons to Metformin in obese T2DM patients

- Surgical treatment (Bariatric surgery) is indicated in patients with BMI >32.5 kg/m^2 with co-morbidity, and BMI >37.5 kg/m^2 without co-morbidity
- Surgical options for weight loss surgery include
  - Restrictive Procedures: Adjustable gastric banding (LAGB) and sleeve gastrectomy
  - Malabsorptive Procedures: Bilio-pancreatic diversions (BPD)
  - Combined Procedures: Roux-en-Y Gastric Bypass (RYGBP)
  - Experimental Procedures: Ileal interposition and duodeno-jejunal bypass, various implantable pulse generator
- Comprehensive lifestyle changes including dietary modification and exercise, behavioral management, pharmacotherapy and bariatric surgery are the most effective interventions for weight management in T2DM patients

Preamble

Obesity is a highly prevalent metabolic disorder that is often associated with T2DM [1]. Obesity is clinically defined as a BMI of ≥30 kg/m^2 (a BMI of 30 represents an overweight of approximately 30 lb. (14 kg) for any given height) [2]. In India, the prevalence of obesity is rising at alarming rate, especially affecting urban population [3]. Indians are at increased predisposition to diabetes that has been attributed to the "Asian Indian Phenotype" characterized by less of generalized obesity measured by BMI and greater central body obesity and more truncal fat as shown by greater WC & waist to hip ratio (WHR) [4-7]. High abdominal obesity contributes significantly to metabolic alterations such as IR, dysglycemia and dyslipidemia[8-12]. Obesity-induced IR may cause T2DM by increasing the allostatic load on the pancreas which eventually leads to failure of pancreas. High consumption of sugars among children and adults in India may also have clinical significance in view of the high tendency for Indians to develop insulin resistance, abdominal adiposity, and hepatic steatosis, and the increasing "epidemic" of T2DM [13]. Because Asians Indians tend to develop diabetes at a significantly lower BMI and WC than white Europeans, lower thresholds of BMI to define overweight (BMI: 23-24.9 kg/m^2) and obesity (BMI ≥25 kg/m^2) were proposed by IDF and NICE [14, 15].

In light of increasing prevalence of obesity in both developed and developing countries and a higher risk for developing IR, dyslipidemia, dysglycemia and a higher cardiovascular risk at lower levels of BMI in Indians, a consensus was convened in New Delhi to redefine the cut-offs for BMI and waist circumference for diagnosing overweight and obesity in Indian population [16]. According to this consensus statement, a BMI of 18 to 23 kg/m^2 should be considered as normal, a BMI of 23-25 kg/m^2 should be considered as overweight, and BMI of more than 25 kg/m^2 should indicate presence of obesity. Similarly the upper limit for waist circumference of men and women was defined as 90 cms and 80 cms respectively.

Considerations

Following local factors were considered when framing guidelines for obesity that were reviewed in Indian context which include: high prevalence of obesity, high abdominal adiposity, increased fasting insulin and insulin resistance, nutritional factors, artherogenic lipid profile [increased triglycerides and low density lipoprotein (LDL) and low HDL].

Rationale and evidence

Identification

- In a cross-sectional study comparison of IDRS and Framingham Risk Score (FRS) by obesity and lipid abnormality status in women of Asian Indian origin hinted that IDRS can predict cardiovascular and diabetic risk more effectively than FRS and serve as simple and cost effective tool for a primary care physician to identify at risk individuals for diabetes and cardiovascular diseases [17].

Exercise therapy

- Bodyweight has been shown to be inversely associated with physical activity and subjects with low physical activity have three-times the possibility of relapse over a 10-year follow-up period compared to those reportedly physically active [18,19]. Moreover the resting metabolic rates appears to be increased by 10% and 5% in aerobic and resistance trained individuals, respectively [20]. Further, slow and prolonged exercise are associated with fatty acid oxidation with beneficial effects on body weight [21].
- Therefore the panel opined that prescribing a combination of aerobic and resistance training exercises in individuals with T2DM can improve metabolic control while reducing the obesity and its related complications.

Pharmacotherapy for obese type 2 diabetes

- Though lifestyle modifications are effective in preventing relapse, they often fail requiring initiation of pharmacotherapy. Metformin is the first choice of drug with some evidence for weight loss [22]. Use of GLP-1analogues

[23] and SGLT-2 inhibitors [24] have been shown to induce weight loss and should be considered as add-on to metformin in obese T2DM patients.

- Orlistat (tetrahydrolipstatin), a lipase inhibitor, is the only approved agent for weight loss in India. It causes modest weight loss by blocking fat absorption from gut, and when used in combination with lifestyle changes was found to be effective in prevention of diabetes [6,25].

Surgery

- Surgical treatment (Bariatric surgery) is indicated in patients with BMI >32.5 kg/m^2 with co-morbidity, and BMI >37.5 kg/m^2 without co-morbidity who fail to lose weight with medical management, [16] although hard evidence for this is lacking. Evidence from several studies suggests that bariatric surgery provides durable glycemic control compared with intensive medical therapy [26-28]. Moreover, gastric bypass has been observed to uniquely restore the pancreatic β-cell function and reduce truncal fat, thus reversing the core defects in diabetes [26].
- Bariatric surgery is an effective option for severely obese patients with poor control T2DM, weight loss due to gastric bypass surgery is associated with good glycemic control [29]. In patients undergone bariatric surgery, about 8% of participants showed complete remission of DM while more than 90% of patients showed a significant decrease in their insulin or oral antidiabetic agents (OADs) demand [29]. Laparoscopic sleeve surgery, a new bariatric surgery is found to be safe and effective treatment option among the obese Indian type 2 diabetes population with significant remission rates ($p<0.001$), larger reductions in HbA1c, and diabetes medication usage [30].

Behavioral therapy

- These include modifiable factors such as eating patterns and exercise habits that can have significant impact on the management of obesity. IDF 2006, recommends in obese T2DM patients to maintain healthy lifestyle through behavioral therapy that includes moderate calorie restriction to promote weight loss (5–10% loss of body weight in the first year) [31], moderate increase in physical activity and change in dietary composition. Other important components of behavioral therapy embraces self-monitoring, goal setting and stimulus or cue control. Such strategies help in setting up realistic goals, guide patients in identifying stimulus that leads to excessive nutrient intake and eliminate them accordingly [32].

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Diet therapy

RSSDI 2015 recommendations

Recommended care

- High-carbohydrate diets with relatively large proportions of unrefined carbohydrate and fiber such as legumes, unprocessed vegetables and fruits are recommended. Brown rice is preferred to polished white rice
- Protein intake equivalent to at least 15% of daily total calories is recommended
- Intake of non-nutritive artificial sweeteners in moderate amounts may be considered
- Combining foods with high and low glycemic indices, such as adding fiber-rich foods to a meal or snack, improves the glycemic and lipaemic profiles
- Cardio-protective Diet should include:
  - More: leafy vegetables, vegetable salads, coarse grains, sprouted grams, spices and all other foods, which are rich in fiber and antioxidants

  - Moderate amounts of: low fat milk and milk products, vegetable oils with monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA), flesh foods (fish, chicken without skin, white of the egg) and artificial sweeteners
  - Avoid: Alcohol, sugar, saturated fats and foods that are refined, processed, salt-rich, cholesterol-rich and deep-fried, polished rice, high fructose corn syrup
  - Total dietary salt intake should be reduced (<5g/day) in population at high risk of hypertension.

- Provide access to a dietician (nutritionist) or other healthcare professionals trained in the principles of nutrition, at or around the time of diagnosis offering an initial consultation with follow-up sessions as required, individually or in groups
- Individualize advice on food/meals to match needs, preferences, and culture
- Advise on reducing energy intake and control of foods with high amounts of added sugars, fats or alcohol
- Provide advice on the use of foods in the prevention and management of hypoglycemia where appropriate

Limited care

- Nutritional counselling may be provided by someone with training in nutrition therapy, but not necessarily a credentialed dietician (nutritionist)

Preamble

Nutritional/diet therapy has been and remains an integral part of diabetes management. As there is no "one-size-fits-all" meal plan or eating pattern, ADA emphasizes on development of individualized eating plan [1] based on individual's health needs, personal and cultural preferences, access to healthful choices, health literacy and numeracy while attaining individualized glycemic goals [2,3]. The primary goal of the diet therapy is to improve health by providing calories for normal growth and development while achieving and maintaining optimal glycemic and normalizing dyslipidemia [4]. Therefore, diets are often altered/modified with respect to amount of carbohydrate, the type of fat and quantity and type of protein to meet these needs. Evidence from epidemiological and experimental studies, focusing on nutritional intervention in the prevention of T2DM suggests that intake of non-starch polysaccharides, omega-3 fatty acids and low glycemic index (GI) foods may play a protective role and high intake of saturated fats and transfatty acids may contribute to the increased risk [5]. However the exact nature of diet most appropriate for patients with T2DM still remains a matter of debate due to lack of tools and strategies that help to decide on healthy eating patterns to minimize the burden of disease [6]. Among South Asian Indians intake of carbohydrate, saturated fatty acids (SFA), trans fatty acids (TFA) and n-6 poly unsaturated fatty acids (PUFA) is higher, and intake of n-3 PUFA and fiber is lower compared to other populations [7]. In addition, attitudes, cultural differences and religious and social beliefs and imbalances in dietary patterns pose significant barriers in effective prevention and management of T2DM in South Asians [8]. Evidence suggests that intake of MUFAs among Asian Indians ranged from 4.7% to 16.4% that indirectly contribute to increasing obesity, metabolic syndrome and T2DM [9,10]. In this context it is felt that RSSDI recommendations on diet therapy can suggest approaches to the dietary management of diabetes in Asian Indians (Annexure II).

Considerations

The panel endorsed most of the IDF recommendations on diet therapy with a few modifications based on the local factors that were reviewed in Indian context including high prevalence of both obesity and undernutrition, poor access to healthy food choices, inadequate physical activity.

Rationale and evidence

High-carbohydrate, low-fat diets

- The most beneficial metabolic profile is provided by a high-carbohydrate low-fat diet, and the worst metabolic profile results from low-carbohydrate high-fat diets.
- High-carbohydrate diabetic diets are effective when relatively large amounts of unrefined carbohydrate and fiber are included such as legumes, unprocessed vegetables and fruits.
- Carbohydrate intake is intertwined with fat intake, and low carbohydrate diets usually tend to be high fat and/or high protein. Fat intake should occur mainly in the form of MUFA with a parallel decrease in SFAs and TFAs. Such a diet is particularly beneficial in patients with impaired glucose tolerance, diabetes and obesity.
- Evidence suggests that in patients with diabetes, the weight loss achieved due to intake of low-carbohydrate diets is linked to duration of the diet restriction and reduced energy intake, but not with restriction of carbohydrates alone. Therefore, obese diabetes patients should consider switching to a diet reduced in calories and fat to reduce the incidence of T2DM and myocardial infarction [11].
- Asian Indians tend to consume high-carbohydrate diets in the form of refined grain. Data from Chennai Urban Rural Epidemiological Study (CURES) suggests that higher consumption of refined grains is significantly associated with higher waist circumference ($p<0.0001$), systolic

blood pressure (p<0.0001), diastolic blood pressure (p=0.03), fasting blood glucose (p=0.007), serum triglyceride (p<0.0001), low high-density lipoprotein cholesterol (p<0.0001), and insulin resistance (p<0.001). Individuals who consumed refined grains were more likely to have metabolic syndrome [odds ratio (OR), 7.83; 95% confidence interval, 4.72-12.99] and insulin resistance compared to those who did not consume [12].

- In another study that examined the association of dietary carbohydrates and glycemic load with the risk of T2DM among an urban adult Asian Indian population, consumption of refined grain [OR 5.31 (95 % CI: 2.98, 9.45); p<0.001], total carbohydrate [OR 4.98 (95 % CI: 2.69, 9.19), p<0.001], glycemic load [OR 4.25 (95 % CI: 2.33, 7.77); p<0.001] and glycemic index [OR 2.51 (95 % CI: 1.42, 4.43); p=0.006] were positively associated with the risk of T2DM while dietary fiber intake was inversely associated with T2DM [OR 0.31 (95 % CI: 0.15, 0.62); p<0.001] [13].
- Data from a population-based, cross-sectional study reporting dietary intake of urban adults living in Chennai, South India indicate that Carbohydrates were the major source of energy (64%), followed by fat (24%) and protein (12%) among South Indian population. Refined cereals contributed to the bulk of the energy (45.8%), followed by visible fats and oils (12.4%) and pulses and legumes (7.8%). Intake of micronutrient-rich foods, such as fruit and vegetable consumption (265 g/d), and fish and seafood (20 g/d), was far below the FAO/WHO recommendation. This suggests that the dietary patterns among urban South Indians contribute to the risk diabetes in this population [14].
- Evidence suggests that improving the carbohydrate quality of the diet by replacing the common cereal staple white rice with brown rice could have beneficial effects on reducing the risk for diabetes and related complications. It was observed that consumption of brown rice was associated with significant reduction in 24-hour glycemic response (p=0.02) and fasting insulin response (p=0.0001) among overweight Asian Indians [15].

Low glycemic index of pulses and pulse-incorporated cereal foods

- Dal Roti, Rice Curry are the typical examples of Indian mixed diets, uniquely different from basic or less-mixed diets of Westerners, Black Africans and other Asians. Different carbohydrate foods mixed with cereals, exhibit GIs intermediate between the GIs of each food individually. Within-individual variations in GI and insulinaemic indices of cereal-pulse mixtures were attributable to viscosity of food, high un-absorbable carbohydrate content or delayed gastric emptying [16].
- Evidence suggests that replacing high GI diets with low GI diets combined with grams and pulses as staple will ensure satiety and adequate calories. Combining acarbose with such modified diet was associated with significant decline in postprandial blood glucose in T2DM patients with secondary failure with OADs [17].
- Similarly, use of Thepla (wheat flour, Bengal gram flour and oil) was associated with lower hyperglycemic and hyperinsulinemia effect in T2DM patients. Enhanced insulin secretion by pulses (gram flour), is attributed to the lower GI of mixed diets in non-insulin dependent diabetes patients [18].
- A retrospective analysis showed that modified pulse-carbohydrate (75% pulse + 25% cereals) was associated with significant reduction in HbA1c (p<0.01) and greater reduction in bodyweight compared to standard diet (75% cereals + 25% pulse) [19].

Consumption of oils among Indian population

- In a recent study evaluating the risk of MS with type of vegetables oils used for cooking among Asian Indians suggest that the prevalence of MS was higher among sunflower oil users (30.7%) than palmolein (23.2%) and traditional oil (17.1%, p<0.001) users. Higher linoleic acid percentage, Vitamin E and linoleic acid/alpha-linolenic acid ratio in sunflower oil was assumed to contribute to increased risk of MS among Asian Indians [20].
- Dietary intervention with cooking oils containing high concentration of monounsaturated fatty acids (canola and olive oil) compared to commonly used refined oils in Asian Indians with non-alcoholic fatty liver disease was associated with significant improvements in grading of fatty liver (p<0.01), liver span (p<0.05), measures of insulin resistance (in olive group) (p<0.001), and lipids [high density lipoprotein in olive group; P=0.004 and triglyceride in the canola oil group; P=0.02] [21].

Fiber and diabetes mellitus

- Fiber rich diet has got a definite role in the treatment of diabetes mellitus, obesity and hypercholesterolemia or hyperlipidemia [22]. The beneficial effects of fiber-rich food in diabetic patients may be attributed to slow release of the absorbed glucose into the blood circulation resulting in decreased insulin secretion [23].
  - Diabetic patients on high carbohydrate and fiber diets were found to have lower post prandial glycemia and serum insulin concentration.

- In obese diabetes patients, diet rich in fiber is particularly useful as it increases satiety reducing the food intake and also shows blood glucose reducing effect as is manifested by a diminished GI.
- Evidence suggests that high fiber diet lowers fasting blood glucose levels ($p<0.01$) and decreases the ratio of low-density lipoproteins to high-density lipoproteins ($p<0.025$) [24].

High prevalence of hypertension among Indian population: need for cardio-protective diet [25] (Annexure III)

- The mean dietary salt intake (8.5g/d) among urban South Indians is higher than currently recommended by the WHO (<5g/d). Higher intake of salt was significantly associated with higher prevalence of hypertension ($p<0.0001$) and increased systolic and diastolic blood pressure ($p<0.0001$). This calls for urgent steps to decrease salt consumption of the population at high risk [26].
- Evidence from CURES indicate that higher intake of fruit and vegetables was associated with significant reduction in systolic blood pressure ($p=0.027$), BMI ($p<0.0001$), waist circumference ($p<0.0001$), total cholesterol ($p=0.017$) and LDL-cholesterol concentration ($p=0.039$). This suggests that increased intake of fruit and vegetable may have protective role against CVD risk in Asian Indians who have high rates of premature coronary artery disease [27].
- Lifestyle and dietary modifications are recommended as first-line management therapies for lipid and glucose control in diagnosed diabetes patients or those with confirmed cardiovascular disease (CVD). In newly diagnosed T2DM patients, initial dietary therapy substantially reduced plasma triglyceride, marginally improved total cholesterol and sub-fractions, and resulted in a potentially less artherogenic profile suggesting that healthy dietary habits help reduce the occurrence and mortality due to CVD events in people with and without established CAD [28, 29].
- It has been observed that, combining foods of known GIs can alter the glycemic and lipaemic profiles favorably, i.e. differences between foods of high and low glycemic indices may be kept minimal [30,31]. Addition of dietary fiber such as dicoccum wheat to the regular diet was associated with significant reduction in total lipids ($p<0.01$), triglycerides ($p<0.01$) and LDL-cholesterol ($p<0.05$) and effectively reduced cardiovascular risk factors [32].
- Evidence from a 24 week randomized control trial in Asian Indians, suggests that single food intervention with pistachio nuts have beneficial effects on the cardio metabolic profile in terms of significant improvements in WC ($p<0.01$), FPG ($p<0.04$), total cholesterol ($p<0.02$), LDL cholesterol ($p<0.006$), high sensitivity C-reactive protein ($p<0.05$), tumor necrosis factor-α ($p<0.03$), free fatty acids ($p<0.001$), thibarbituric acid reactive substances ($p<0.01$) and adiponectin levels ($p<0.001$) [33].

Indian consensus dietary guidelines to prevent obesity, metabolic syndrome and diabetes

- Excess consumption of calories, saturated fats, transfatty acids, simple sugars, salt and low intake of fiber together with sedentary lifestyles led to increase in obesity, T2DM, CVD in both urban and rural populations of India [34]. In light of this, consensus dietary guidelines for Asian Indians were framed with an intention to curb rising epidemics of obesity, the MS, hypertension, T2DM, and CVD. The consensus guidelines emphasize on
  - reduction in the intake of carbohydrates,
  - preferential intake of complex carbohydrates and low glycemic index foods,
  - higher intake of fiber,
  - lower intake of saturated fats,
  - optimal ratio of essential fatty acids,
  - reduction in trans fatty acids,
  - slightly higher protein intake,
  - lower intake of salt,
  - restricted intake of sugar less than 10% of total daily energy intake [35]

Diet-related non-communicable diseases (NCDs) in India

- Studies evaluating secular trends in dietary intake in relation to NCDs in India suggest that, over the past 3 decades (1973–2004) a rapid transition in nutrition occurred with concurrent increase in including obesity, hypertension, metabolic syndrome, T2DM, and CAD. Evidence indicate that there was a 7% decrease in energy derived from carbohydrates and a 6% increase in energy derived from fats. Decreased intake of coarse cereals, pulses, fruits and vegetables, together with increased intake of meat products and salt, coupled with declining levels of physical activity resulted in escalated burden of NCDs in India [36].

Implementation

Implementation of dietary management therapies demands knowledgeable and competent dietitians/nutritionists who are trained in providing effective dietary interventions that are in consistency with individual's needs and demands. Self-management and counselling in nutrition (for individuals

or groups) should include assessment, identification of the nutrition problem, and implementation of nutritional strategies, nutrition monitoring and evaluation of outcomes. Nationwide community intervention programs aimed at creating awareness about the consequences of unhealthy food choices and replacing them by healthy food choices is urgently needed in India. Evidence from initial studies suggests that simple 4-week nutritional counselling provided to increase patient's nutritional knowledge can significantly improve fasting and post prandial blood glucose levels in illiterate to semi-literate patients with T2DM [37]. Increasing taxation on sugar-sweetened beverages have been shown to decrease the incidence of obesity and T2DM, suggesting that prevention strategies, encompassing multiple stakeholders (government, industry, and consumers), may decrease sugar consumption in the Indian population [35].

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Lifestyle management

RSSDI 2015 recommendations

Recommended care

- Offer lifestyle advice to all people with type 2 diabetes around the time of diagnosis.
- Review and reinforce lifestyle modification yearly and at the time of any treatment change or if feasible at every visit.
- Review and provide ongoing counselling and assessment yearly as a routine, or more often as required or requested, and when changes in medication are made.
- Advise people with type 2 diabetes that lifestyle modification, by changing patterns of eating and physical activity, can be effective in controlling many of the adverse risk factors found in the condition.
- Introduce physical activity gradually, based on the individual's willingness and ability, and setting individualized and specific goals.
- A total of 60 min of physical activity is recommended every day for healthy Indians in view of the high predisposition to develop T2DM and CAD
  - at least 30 min of moderate-intensity aerobic activity
  - 15 min of work-related activity
  - 15 min of muscle-strengthening exercises (at least 3 times/week)
- In the absence of contraindications, encourage resistance training three times per week.
- Provide guidance for adjusting medications (insulin) and/or adding carbohydrate for physical activity.
- Yogic practices lead to improvement in glycemic control, reduction in BP, Correction of dyslipidemia, Reduction of insulin resistance and correction of hyperinsulinemia, with elimination of stress
- Yogic practices can be combined with other forms of physical activity when it should be done for 30 min every day while for those individuals not having other forms of

physical activity, it is recommended that yogic practices are carried out for 45-60 min to achieve the metabolic benefits

Limited care

- The principles and content of lifestyle management are as for *recommended* care.
- Encourage increased duration and frequency of physical activity (where needed), up to 30-45 minutes on all days of the week, or an accumulation of at least 150 minutes per week of moderate-intensity aerobic activity (50-70% of maximum heart rate).

Preamble

Lifestyle management is an integral part of diabetes management along with dietary and pharmacological interventions. Obesity, one of the foremost reasons for the development of T2DM and associated with higher CV risk, can be controlled with significant lifestyle modifications. The major forms of lifestyle modifications considered for patients with T2DM include: diet and physical activity (both aerobic and resistance training). Wealth of literature supports the cause of regular physical activity in reduced morbidity and mortality in patients with T2DM. Regular aerobic training not only reduces glycemic burden but also helps prevent atherosclerotic CVD by several mechanisms. In older adults with diabetes, regular walking was associated with reduced all-cause death [1]. Interestingly, practicing physical activity is shown to provide similar benefits in patients with T2DM whether exercises are done in single or multiple bouts, as long as the recommended length of activity is performed. Recent reports indicate positive effects of resistance training in patients with T2DM. With appropriate caution, all T2DM patients with complications can perform mild-moderate physical activity. Yoga is also known to reduce glycemic parameters, improve insulin sensitivity, decline insulin resistance, and reduce the use of OADs [2]. Since Asians are considered to do less physical activity compared to their western counter parts [3], lifestyle modification is of paramount importance for blood glucose control and cardiovascular protection in patients with T2DM.

Considerations

The panel endorsed most of the IDF recommendations on Lifestyle modifications with additions on the specific role of yoga in the Indian context. The panel considered evidences of physical activity on glycemic parameters in view of the high predisposition of Asian Indians to develop T2DM and CAD. The benefits of yogic practices, individually and when combined with physical activity are also considered.

Rationale and evidence

Physical activity

- Hepatic glucose production and peripheral glucose uptake maintain glucose homeostasis in the resting fed state. However, due to the progressive insulin resistance, both the phenomenon are affected, causing hyperglycemia. Moreover compared to other ethnic groups, Asian Indians are more prone to metabolic syndrome and insulin resistance at a relatively young age [4,5].
- Physical activity tends to increase the blood flow to the muscles resulting in increased uptake of glucose and oxygen. The effects of aerobic training on glycemic control are well established. Adults with T2DM following a simple aerobic walking program reported a significant decrease in glycemic parameters (HbA1c and FPG) as well as BMI and general well-being [6].
- Short-term progressive resistance training program either in untrained or supervised training have shown to significantly decrease elevated blood glucose levels, lipid parameters, and body weight in Asian Indians with T2DM [7,8].
- A recent meta-analysis examined the effects of combined training (CT) of aerobic training (AT) and resistance training versus AT alone on HbA1c reduction and other physiological parameters, in patients with T2DM. Data from seven studies including 192 male and 240 female patients revealed that CT decreased glycemic burden, abdominal adipose tissue, lipid profile (total cholesterol, and triglycerides) with no effect on adverse events or study withdrawal [9].
- T2DM patients with sedentary lifestyle in whom structured aerobic exercise is not feasible, practicing resistance training and home based walking was found to be safe, effective and beneficial with significant decrease in HbA1c ($p<0.05$), FPG as well as depression and quality of life [10].
- Physical activity is also known to ameliorate the overall health status, depressive symptoms and decrease the rate of hospitalizations in patients with T2DM. A 2-year follow-up study in T2DM patients reported that physical activity status is an independent predictor of lower hospitalizations and an important strategy to reduce health care costs [11].
- However, for the resource limited settings, the IDF guideline for T2DM encourages increased duration and frequency of physical activity (where needed), up to 30-45 min on 3-5 days/week, or an accumulation of 150 min/week of moderate-intensity aerobic activity (50-70%

of maximum heart rate) [12]. These recommendations were discussed and a balanced recommendation was framed based on the vast experience of panel members.

- Further, in view of the high predisposition of Asian Indians to develop T2DM and CAD, the recent consensus physical activity guidelines for Asian Indians, provide preventive measures: a total of 60 min of physical activity every day [13] although hard evidence for a clear benefit of this in Indians is lacking. This can include:
  - at least 30 min of moderate-intensity aerobic activity
  - 15 min of work-related activity
  - 15 min of muscle-strengthening exercises
- Based on the previous guidelines, the RSSDI statement, in its previous version, recommend all patients with T2DM to perform with regular exercises (Annexure IV), either mild or moderate intensity.

Yoga

- Another important way of overcoming the chronic stress and negative affective state in patients with T2DM is through mind-body therapy, especially the 'Yoga' [2]. Yoga is an old, traditional, Indian psychological, physical and spiritual exercise regimen [14].
- In view of the resource constraints and diversity in lifestyles among Indian population, yoga appears to be a suitable alternative to supplement to lifestyle intervention programs that are close to population. Yoga, as a practice is a holistic philosophy, in which physical exercises are intertwined with lifestyle and behavioral changes of the community, including diet, relaxation, and stress management.
- It has been previously documented from studies on healthy individuals that long-term practice of yoga leads to lower metabolic rates [15], lower levels of the stress hormone cortisol [16], changes in the activity of the autonomous nervous system [17], and increases in insulin secretion [18].
- Practicing yoga and pranayama for a period of 3 months in uncomplicated patients with T2DM showed beneficial effects on metabolic parameters [HbA1c, FPG, and post prandial glucose (PPG)] and anthropometric measurements [19]. In addition, yogasanas tend to exhibit positive effect of on glucose utilization and fat redistribution in these patients [20]. Patients practicing specific yogasanas for up to 40 days responded with significant decrease in FPG, PPG, waist-hip ratio and changes in insulin levels.
- Evidence also suggests that beneficial effects of yoga goes beyond glycemic control with clinical improvement in nerve function observed in mild to moderate T2DM with sub-clinical neuropathy [21]. In patients practicing specific yogasanas for up to 40 days, the right hand and left hand median nerve conduction velocity has increased from 52.81 +/- 1.1 m/sec to 53.87 +/- 1.1 m/sec and 52.46 +/- 1.0 to 54.75 +/- 1/1 m/sec, respectively.
- As there is a possibility of vitreous hemorrhage with pranayama like Kapaal Bhatti, one should exercise caution when performing these asanas.
- In view of the evidences on beneficial effects of physical activity and yoga, the expert panel opined a combined approach would incur more beneficial effects in controlling metabolic as well as physiological measures in patients with T2DM.
- Currently the role of yoga and fenugreek in the prevention of diabetes is being evaluated in the Indian prevention of Diabetes Study by RSSDI.

Implementation

Implementation of life style management in patients with T2DM requires adequate awareness and education from the treating physician. It is imperative that all healthcare professionals encourage patients to practice the combined approach of diet, physical activity along with pharmacological intervention. In this regard, providing patients with structured educational programs using information leaflets on practices and procedures of physical activity could greatly enhance the adherence and overall health of patients with T2DM.

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Education

RSSDI 2015 recommendations

Recommended care

- Make patient-centered, structured self-management education an integral part of the care of all people with type 2 diabetes:
  - From around the time of diagnosis
  - On an ongoing basis, based on routine assessment of need
  - On request
- Use an appropriately trained multidisciplinary team to provide education to groups of people with diabetes, or individually if group work is considered unsuitable. Where desired, include a family member or friend
- Include in education teams a health-care professional with specialist training in diabetes and delivery of education for people with diabetes
- Ensure that education is accessible to all people with diabetes, taking account of culture, ethnicity, psychosocial, and disability issues. Consider delivering education in the community or at a local diabetes center, through technology and in different languages. Include education about the potential risk of alternative medicine
- Use techniques of active learning (engagement in the process of learning and with content related to personal experience), adapted to personal choices and learning styles
- Use modern communications technologies to advance the methods of delivery of diabetes education
- Provide ongoing self-management support

Limited care

- The principles are as for Recommended care but education may be provided by a smaller team (physician and educator) or in very limited situations by an appropriately skilled individual
- Consider how available technologies can best be used to deliver education

Preamble

Education is recognized as an important component of management of T2DM. Individuals with diabetes tend to make dramatic impact on the progression and development of diabetes by involving in their own diabetes self-care practices [1]. It is expected that patient who is well-educated have better understanding of the disease and self-manage the condition more effectively [2]. Evidence from literature suggests that implementation of diabetes self-management education (DSME) have been successful in lowering glycemic levels in uncontrolled patients [3]. DSME is an ongoing process that facilitates knowledge, skill and ability necessary for diabetes self-care [4]. It is guided by evidence based standards while incorporating needs, goals and life-experiences of the person with diabetes [5]. India is a country with diverse social, economic, cultural, and educational patterns with majority of population residing in rural areas. It is expected that, the level of awareness on diabetes is poor in India due to sheer numbers of individuals with low or no literacy [6,7].

Considerations

The panel endorsed the IDF recommendations on education as such. However scanty evidence from India together with local factors such as cost, literacy, malnutrition, bodyweight and BMI were reviewed in the Indian context and were reflected in the recommendations.

Evidence

Educational programs and their outcomes

- In management of T2DM patient, structured diabetes care program (Freedom 365*) of on-going diabetes education on diet and lifestyle correction, biochemical investigations, clinical monitoring and treatment at regular intervals was associated with better clinical outcomes compared to routine medical care. The program played a pivotal role in improving the patient's quality of care by overcoming clinical inertia, improving adherence to therapy while preventing the occurrence/progression of diabetic complications [8].
- Organized diabetic education, that involves improving knowledge on better control of disease symptoms, disease regimens and dangers in practice, was found to positively impact lifestyle changes, self-control abilities, and at the same time improve the quality of life in T2DM patients [9].
- The National Diabetes Educator Program (NDEP) course was designed to enable educators in India to provide a complete perspective of the disease condition, the importance of self-care, blood glucose monitoring, diet, and physical activity, self-injection of insulin, medication adherence, and the long-term benefits of compliance and a basic awareness of the various complications of diabetes. Following its implementation, most of participants acknowledge that they learned new skills and they were benefited by increase in knowledge, confidence and improved attitude toward diabetes care among the participants [10].
- Besides diabetes, educational intervention was also successful in reducing some of the obesity parameters and improving dietary patterns in individuals with prediabetes and diabetes. Initiation of preventive education right from elementary schools could reduce impaired fasting glucose by 17% suggesting such interventions may delay T2DM or even change the course of disease for improved outcomes among vulnerable population groups [11].

Knowledge and awareness

- Though general practioners in India are well aware and updated about symptoms and screening of T2DM, there is lack of effective approach towards screening and treatment of complications. Most of the patients were not advised on non-pharmacological measures and diabetes education while interpretation of test results for screening of disease and its complications appeared to be major flaw in general practice [12].
- Evidence from several studies determining the level of knowledge and awareness on diabetes across India suggest that most of the patients had poor knowledge and awareness about their condition [13-20]. Low socioeconomic status, old age, cultural factors, lack of access to healthcare, family history of diabetes and importantly low literacy levels were the major predictors of poor glycemic control among patient with T2DM.

Challenges in diabetes management in India [21,22]

- The awareness about the disease and its complications is also less than satisfactory.

- Lack of Knowledge Attitude Practice studies to determine the gaps in knowledge among diabetics and physicians in the areas of Individual Diabetes Care in India.
- Inadequate knowledge, delay in clinical response and poor control are some of the physician-related issues that needs to be addressed through diabetes education.
- Patients' lack of knowledge about diabetes care is a significant barrier that can impede their ability to manage their disease. In view of this, there is an imperative need for more structured diabetes education programs in India.
- Lack of strong referral system to provide quality care i.e. early diagnosis, prevention and control of chronic complications in diabetes.

Assessing the need for evidence-based education [23,24]

- Continuous medical education, additionally trainings are needed to help health professionals integrate new knowledge and transform old practices.
- Need to assess the impact of existing education and training programs in diabetes.
- Investment must be made to ensure specialized diabetes education is accessible to healthcare personnel and people with diabetes.
- General practitioners and physicians should be updated on recent guidelines on diagnosis, treatment as well as management goals.
- Steps to improve awareness in diabetes care:
  - Physician Education
  - Need for Continuing Medical Education
  - Patient Education
  - Diabetes Education Programs in India
- Counselling is the most important strategy capable of bringing about sustained lifestyle changes [25].

Implementation

- Major components of implementing these recommendations are the recruitment of personnel and their training in the principles of both diabetes education and behavior change strategies. The staff are required to develop theoretically based, patient centered, ongoing follow up education programs for people with diabetes. Educational strategies and materials matched to the needs and culture of the community served with attention to health literacy are necessary. Institutional support at the practice, community and health system levels is critically important.

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Oral antidiabetic agents

RSSDI 2015 recommendations

Recommended care

- Begin oral glucose lowering medications when lifestyle interventions alone are unable to maintain blood glucose control at target levels
  - Maintain support for lifestyle measures throughout the use of these medications
  - Consider each initiation or dose increase of an oral glucose lowering medications as a trial, monitoring the response in 2-3 months
  - Consider cost and benefit: risk ratio when choosing a medication
  - Consider discontinuing ineffective therapies
  - Hypoglycemia, weight gain and cost of therapy are also important parameters in deciding therapy

- First-line therapy
  - Begin with metformin unless there is evidence of renal impairment or other contraindication
  - Titrate the dose over early weeks to minimize discontinuation due to gastrointestinal intolerance
  - Monitor renal function and use metformin with caution if estimated glomerular filtration rate (eGFR) <45 ml/min/1.73 m^2
  - Other options include a sulfonylurea (or glinide) for rapid response where glucose levels are high, or a DPP-4 inhibitor or alpha glucosidase inhibitor; these agents can also be used initially in place of metformin where it is not tolerated or is contraindicated
  - In some circumstances dual therapy may be indicated initially if it is considered unlikely that single agent therapy will achieve glucose targets

- Second-line therapy
  - When glucose control targets are not being achieved, add a sulfonylurea
  - Other options include adding metformin if not used first-line, α-glucosidase inhibitor, a dipeptidyl peptidase 4 (DPP-4) inhibitor or a thiazolidinedione
  - A rapid-acting insulin secretagogue is an alternative option to sulfonylureas
  - SGLT-2 inhibitors can also be considered in second line when weight and hypoglycemia are concerns
  - GLP-1 analogues due to its cost, GI intolerance and mode of administration (injectable) places it a little lower in the list of second line of drugs, especially while treating patients in India. However its weight loosing property and lack of hypoglycemia makes it a favorable option for a limited group of diabetic population

- Third-line therapy
  - When glucose control targets are no longer being achieved, start insulin or add a third oral agent
  - If starting insulin, add basal insulin or use premix insulin
  - If adding a third oral agent options include an α-glucosidase inhibitor, a DPP-4 inhibitor, a SGLT2 inhibitors or a thiazolidinedione
  - Another option is to add a GLP-1 analogues

- Fourth-line therapy
  - Begin insulin therapy in combination with a sensitizing agent (metformin or glitazone) when optimized oral blood glucose lowering medications (and/or GLP-1 analogues) and lifestyle interventions are unable to maintain target glucose control
  - Intensify insulin therapy is already using insulin

Limited care

- The principles are as for Recommended care taking particular note of cost and availability of generic therapies

Preamble

The primary aim of controlling glycemic levels are to avoid acute symptoms of hyperglycemia, to avoid fluctuation in blood glucose over time, and to prevent/delay the development of various diabetic complications without hampering quality of life of patients. The treatment should also aim at preserving beta cell function and prevent or slow the rate of apoptosis that will in turn delay the natural progression of the disease. Particularly from a patient point of view stability of metabolic control over time may be another specific goal that needs to be considered. Given the progressive loss of beta-cell function in T2DM, treatment with OADs is ensued if the target HbA1c is not achieved with initial life style modification. However, the properties of any anti-diabetic agent that play a role in the choice of drug(s) in individual patients may vary because diabetes itself have a different mechanism responsible for its pathophysiology. Several guidelines provide treatment algorithms on ways in which glucose-lowering agents can be used either alone or in combination. The current guideline based on the current clinical evidences provides overview on available OADs and tries to come up with some practically applicable recommendations for optimal management of diabetes in Asian Indians.

Considerations

The decision on choice of OAD therapy in T2DM patients was based on the cost and efficacy factors that were reviewed in Indian context.

Rationale and evidence

Anti-diabetic agents

- *Biguanide:* Metformin remains the first-line type 2 diabetes drug due to its properties such as efficacious, weight neutral, economical, devoid of major adverse effects such as hypoglycemia etc. Its mechanism of action predominately involves reducing hepatic glucose output [1,2]. Metformin is associated with initial gastrointestinal side effects, and caution needs to be taken to avoid its use in patients at risk for lactic acidosis (e.g. in advanced renal insufficiency, alcoholism). Even some cardiovascular benefits from this drug that has been noted, but the clinical trial data are not robust.
- *Sulfonylurea:* It is the oldest oral hypoglycemic agent class also known as insulin secretagogue. They show their effect by closure of ATP-sensitive potassium channels on beta cells, these drugs stimulate insulin release [3]. Although they are effective in controlling glucose levels, but their use is associated with modest weight gain and risk of hypoglycemia. The modern sulfonylureas particularly Gliclazide MR and also glimepiride have a lower risk of hypoglycemia and are the preferred sulfonylureas to be used. Glibenclamide should be used only in case of non-availability of these agents. In addition, studies have demonstrated that chances of secondary failure with this drug that may exceed other drugs, which could be due to an exacerbation of islet dysfunction [4]. Shorter-acting secretagogues, the meglitinides (or glinides), also stimulate insulin release through similar mechanisms but may be

associated with comparatively less hypoglycemia [5] but they require more frequent dosing.

- *Thiazolidinediones:* TZDs are also recognized as peroxisome proliferator activated receptor γ activators [6] that improve insulin sensitivity in skeletal muscle and reduce hepatic glucose production [1,2]. The risk of hypoglycemia is negligible and may be more durable in their effectiveness than sulfonylureas and metformin [4]. Pioglitazone appeared to have a pleotropic effects on cardiovascular events as a secondary outcome in one large trial involving patients with overt macrovascular disease [7]. Pioglitazone had recently been linked with a possible increased risk of bladder cancer [8] but it was not substantiated. Data from a retrospective study in India involving 2222 (pioglitazone users, n=1111 and pioglitazone non-users, n=1111) T2DM patients found no evidence of bladder cancer in any of the group, including patients with age >60 years, duration of diabetes >10 years and uncontrolled diabetes [9].Recognized side effects of TZDs include weight gain, fluid retention leading to edema and/or heart failure in predisposed individuals and increased risk of bone fractures [4,7].
- *Incretin mimetics:* The injectable GLP-1 receptor agonists or Incretin mimetics mimic the effects of endogenous GLP-1, thereby stimulating pancreatic insulin secretion in a glucose dependent fashion, suppressing pancreatic glucagon output, slowing gastric emptying and decreasing appetite. Their main advantage is weight loss, which is modest in most patients but can be significant in some of the patients. A limiting side effect is nausea and vomiting, particularly early in the course of treatment. There have been concerns regarding an increased risk of pancreatitis, but recently published ELIXA study did not show any increased risk of pancreatitis, pancreatic cancer or thyroid cancer with lixisenatide [10]. The oral dipeptidyl peptidase IV (DPP-4) inhibitors or Incretin enhancer enhance circulating concentrations of active GLP-1 and GIP [11, 12]. Their major effect appears to be in the regulation of insulin and glucagon secretion; they are weight neutral. Furthermore, recent cardiovascular studies with DPP-4 inhibitors have shown that these agents do not increase the CV risk [13-15]. Typically, none of the incretin-based classes cause hypoglycemia by themselves.
- *Sodium–glucose cotransporter 2:* SGLT-2 inhibitors provide insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT-2. These agents provide modest weight loss and blood pressure reduction. Although there are two FDA approved agents for use in patients with type 2 diabetes, there are insufficient data to recommend clinical use in type 1 diabetes at this time [16]. SGLT-2 inhibitors have the potential to reduce CV risk in patients with T2DM not only through beneficial effects on glycemic control, but also via beneficial effects on body weight, BP, lipids, and serum uric acid [17]. SGLT-2 inhibitors significantly reduce BP in patients with type 2 diabetes [18].
- Two agents that are used infrequently in treatment course of diabetes are α-glucosidase inhibitors (AGIs), which retard gut carbohydrate absorption [19], and colesevelam, a bile acid sequestrant whose mechanism of glucose-lowering action remains poorly understood and whose major additional benefit is LDL-cholesterol reduction [20]. Both have gastrointestinal effects, mainly flatulence with AGIs and constipation with colesevelam. The dopamine agonist bromocriptine (quick release formulation) is also available as an anti-hyperglycemic agent and supposedly acts by mimicking the morning surge of dopamine [21]. Its mechanism of action and precise role are unclear. The amylin agonist, pramlintide (not available in India), is typically reserved for patients treated with intensive insulin therapy, usually in type 1 diabetes mellitus; it decreases postprandial glucose excursions by inhibiting glucagon secretion and slowing gastric emptying [22].
- The glucose-lowering effectiveness of non-insulin pharmacological agents is said to be high with metformin, sulfonylureas, TZDs and GLP-1 agonists (expected HbA1c reduction ~1.0–1.5%) [23-25], and comparatively lower for meglitinides, DPP-4 inhibitors, SGLT-2 Inhibitors, AGIs, colesevelam and bromocriptine (~0.5–1.0%). However, older drugs have typically been tested in clinical trial participants with higher baseline HbA1c, which is associated with greater treatment emergent glycemic reductions, irrespective of therapy type. In head-to-head trials, any differential effects on glucose control are small. So agent- and patient-specific properties, such as ease of administration, dosing frequency, side-effect profiles, cost and other benefits often helps in their selection.

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Insulin therapy

RSSDI 2015 recommendations

Recommended care

- Do not unduly delay the commencement of insulin
- Maintain lifestyle measures, support for work and activities of daily living after introduction of insulin
- Consider every initiation or dose increase of insulin as a trial, monitoring the response
- Explain to the person with diabetes from the time of diagnosis that insulin is one of the options available to manage their diabetes, and that it may turn out to be the best, and

eventually necessary, way of maintaining glucose control, especially in the longer term
- Provide education and appropriate self-monitoring
- Explain that starting doses of insulin are low, for safety reasons, but that eventual dose requirement is expected to be 30-100 units/day
- Continue metformin. Other oral agents may also be continued
- Begin with:
  - A basal insulin once daily such as, insulin glargine or insulin detemir or insulin degludec
    or
  - Once or twice daily premix insulin (biphasic insulin) preferably premixed analogues
- Initiate insulin using a self-titration regimen (dose increases of two units every 3 days) or with biweekly or more frequent contact with a healthcare professional.
- Aim for pre-meal glucose levels of <115 mg/dl
- Monitor glucose control for deterioration and increase dose to maintain target levels or consider transfer to a basal plus mealtime insulin regimen
- Match the timing of insulin and meals
- Provide guidance for adjusting insulin for physical activity
- SMBG on an ongoing basis should be available to those people with diabetes using insulin

Limited care

- The principles are as for Recommended care taking particular note of cost and availability of generic therapies
- Less expensive basal human insulins – neutral protamine hagedron (NPH) insulin and conventional premixed – Human insulin can give most of the health care gains achievable with insulin therapy
- Insulin supplies should be assured and be of consistent quality and type

Preamble

By the time diagnosis is done, patient with T2DM had lost more than 50% of their beta-cell function which steadily continues to decline at approximately 3-5% per year [1]. Most of the medications available to control glycemia have a final common pathway in the form of targeting beta cells or insulin resistance and are dependent upon the presence of insulin for their therapeutic effect. The durability of these medications varies and their safety is occasionally under scrutiny. Overtime, even with multiple OADs patients fail to achieve or maintain HbA1c levels, necessitating insulin therapy. The knowledge available through land mark trials in last decade warrant that glycemic control should be intensive in early stages of diabetes preferably first four years of diagnosis of diabetes [2]. This makes us understand that the indications of insulin therapy in T2DM should be more aggressive, albeit not at the cost of producing severe symptomatic hypoglycemia, especially in a selected group of patients where hypoglycemia may be deleterious. The traditional postponement of insulin therapy after prolonged failure of lifestyle and oral agents to achieve glycemic control has been revised in the last decade to incorporate primarily basal insulin therapy much earlier, often in combination with OADs or GLP-1 receptor agonists. All health care professionals and primary care physicians must understand the significance of legacy effect that was very clearly demonstrated in the long-term cohorts of UKPDS.

Considerations

The decision on choice of insulin therapy in T2DM patients was based on the local factors such as cost and efficacy of insulin therapy and availability of insulin pens and injections that were reviewed in Indian context:

Rationale and evidence

Insulin therapy

- *Insulin*: Due to the progressive nature of diabetes and beta cell dysfunction that characterizes type 2 diabetes, insulin replacement therapy is frequently required [3]. Importantly, most of the patients with T2DM maintain some endogenous insulin secretion even in late stages of disease. Accordingly, the more complex and intensive strategies of type 1 diabetes are not typically necessary [4]. Ideally, the principle of any insulin use is the creation of as normal a glycemic profile as possible without unacceptable weight gain or chances of hypoglycemia [5].
- Initiation of insulin therapy (Annexure V):
  - As initial therapy, unless the patient is markedly hyperglycemic and/or symptomatic, a 'basal' insulin alone is typically added [6]. The general concept is to first correct the fasting hyperglycemia with bed time injection of basal insulin, and then address postprandial hyperglycemia, if needed, with other options.
  - Both AACE/ACE and ADA/EASD guidelines recommend initiating insulin therapy with basal insulin. Similarly, IDF recommends initiation of insulin with either basal insulin (Annexure VI) or premixed insulin (Annexure VII) when combination of oral therapies fail to achieve glycemic target of HbA1c <7.0% [7-9].

- Basal insulin provides relatively uniform insulin coverage throughout the day and night, mainly to control blood glucose by suppressing hepatic glucose production in between meals and during sleep. Either intermediate-acting (neutral protamine hagedron [NPH]) or long-acting (insulin glargine, insulin degludec or insulin detemir) formulations may be used. The latter three are associated with modestly less overnight hypoglycemia than NPH and possibly slightly less weight gain, but are more expensive [10-11]. Of note, the dosing of these basal insulin analogues may differ, with most comparative trials showing a higher average unit requirement with insulin detemir compared to glargine [12].
- Indian insulin guidelines by Indian National Consensus Group (INCG), recommend initiation of insulin in newly diagnosed patients with FPG>250 mg/dl, PPG>300 mg/dl, HbA1c >9% or if patient fails on maximal tolerated/optimal doses of 2 or 3 OADs. If HbA1c levels are between >7% and ≤7.5% after initial treatment with metformin, guidelines recommends second oral agent (OAD/GLP-1 agonist). However, if HbA1c levels still remain above 7% after 3 months of dual therapy, it recommends addition of premixed insulin once (OD) or twice daily (BID) to metformin therapy. If HbA1C levels are >7.5% and ≤8.5%, it recommends addition of premixed insulin OD to initial metformin therapy. It recommends to titration of premixed insulin therapy from OD to BID, if HbA1c levels are above 8.5%. Similarly, HbA1c levels above 7% and FPG >100 mg/dl, requires titration of premixed insulin once/twice daily till FPG levels are below 100 mg/dL [13].
- Premix insulin can be started once daily with 10 U either in the morning, if pre-dinner glucose is high or in the night, if the pre-breakfast glucose is high. If a patient on biphasic insulin aspart (BIAsp) 30 OD or BID has within-target FPG but an HbA1c >7%, a switch to BIAsp 30 BID or TID should be considered. If their FPG is above target, the dose should be titrated to achieve FPG: 72–108 mg/dL; however, if hypoglycemia occurs, an additional daily dose should be added rather than further dose titration [14]. When the daily insulin dose in OD regimen exceeds 20 U, intensify the regimen to BID such that the dose is distributed as two third in morning and one third in evening. However when the single dose exceeds 30 units, the dose can be split into two equal doses, which reduces the chance of hypoglycemia. Also premix insulin may be started twice daily in case of patients with higher HbA1c, or if blood glucose control is suboptimal [13].
- In a 26-week, open-labelled, randomized, parallel-group, multinational, treat-to-target trial in 155 insulin-naïve Asian subjects inadequately controlled with OADs showed that initiation of once-daily biphasic insulin aspart 30 is superior to insulin glargine in terms of HbA1c reduction (p=0.015) and mean self-measured plasma glucose (SMPG) at bedtime (p=0.0078) compared to glargine [15].

- Intensification of insulin therapy (Annexure VIII):
  - Although most of the patients with T2DM requiring insulin therapy can be successfully treated with basal insulin alone, some, because of progressive diminished in their insulin secretory capacity, will require prandial insulin therapy also with shorter-acting insulins. This is typically provided with regular insulin given about 30 mins before meals or rapid insulin analogues such as insulin lispro, insulin aspart or insulin glulisine, which could be given just before the meal. They result in better postprandial glucose control than the less costly human regular insulin, whose pharmacokinetic profile makes it less attractive option in such kind of patients.

- Indications of insulin in T2DM in newly detected patient:
  - Those patients, who at the time of diagnosis are symptomatic and have one of the following:
    - HbA1c more than 9%
    - Fasting hyperglycemia in excess of 250 mg/dl
    - Post prandial hyperglycemia in excess of 300 mg/dl
    - In catabolic stage
    - Ketone positive
  - When patient presents with acute stress like infection, dehydration or acute cardiovascular disease such as acute coronary syndrome or acute myocardial infarction, insulin has the advantage of being effective where other agents may not be. Insulin should be considered as part of any combination regimen:
    - In these cases insulin may be started as monotherapy or with metformin if not contraindicated.
    - As the patient's glucose toxicity resolves, the regimen can, potentially, be subsequently simplified and a switch over to only oral agents may be considered.

- Indications of insulin in T2DM patients with already established diagnosis:
  - If a trial of adequate doses of three non-insulin agents for 6-9 months fails to achieve HbA1c to target levels , addition of insulin may be justified as the landmark studies suggest that achieving intensive glycemic control (if not contraindicated) in initial few years of diagnosis is of profound benefit.

- It has to be understood that during first year of diagnosis, as we do not expect complete insulinogenic and as sulfonylurea is still considered to be the most potent and cheapest of all oral drugs, one of these three (or more) medicines should be sulfonylurea.
- Life style changes including medical nutrition therapy, exercise, smoking cessation must be continued vigorously and education at all stages will be complimentary to the management.
- While initiating insulin, doses of sulfonylurea should be reduced and a strict watch must be kept on occurrence of hypoglycemia.
- HbA1c targets must be determined as per criteria set for individualized therapy [16] and efficacy of each agent of reducing HbA1c as combination therapy must be considered.
- Individualization of therapy requires taking several factors into consideration, including an assessment of the patient's risk for hyperglycemia and related complications versus the risks of therapy, presence of comorbid conditions, assessment of psychological status, capacity for self-care, economic considerations, and family and social support systems. Near-normal glycemic targets should be considered for younger patients with recent onset of T2DM and little or no micro- or macrovascular complications, while, slightly higher HbA1c targets may be considered for older patients with long-standing T2DM and evidence of CVD [17].
- If a patient already on two or more agents, continues to have HbA1c in excess of 9%, Insulin may be initiated even if patient is asymptomatic.
- It should be explained to the patient during every visit following diagnosis of diabetes, that insulin is one of the options available to manage their diabetes, and that it may turn out to be the best, and eventually necessary way of maintaining glucose control, especially in the longer term.
- Adequate doses of oral agents do not necessarily mean the highest administrable doses because in most of the cases, doubling the doses of these medicines does not necessarily increment their effects.
- Weight gain with insulin therapy is inevitable adverse effect. However evidence from a study in T2DM patients, evaluating the effect of different treatment modalities on weight gain indicate that, sulfonylurea (SU) + Insulin (I) was associated with significant weight gain followed by I group, SU group, and SU + metformin (MF) + I group, and SU + MF group. The weight gain on treatment was significantly related to pre-treatment weight loss and patients with improved metabolic control tend to attain stable body weight [18].
- Ideally, an insulin treatment program should be designed specifically for an individual patient, to match the supply of insulin to his or her dietary/exercise habits and prevailing glucose trends, as revealed through self-monitoring. Anticipated glucose-lowering effects should be balanced with the convenience of the regimen, in the context of an individual's specific therapy goals.
- Proper patient education regarding monitoring of glucose, insulin injection technique, insulin storage, recognition/ treatment of hypoglycemia, and 'sick day management is imperative. Where available, certified diabetes educators can be invaluable in guiding the patient through treatment course of diabetes.

Implementation

Lifestyle measures, self-monitoring and education, should be integral parts of maintaining glucose management practices that will enhance the effectiveness of blood glucose lowering therapies. Avoiding delay in starting insulin therapy has been problematic in nearly all diabetes services. Structured guidelines and protocols and audit of glucose control of people on oral medications should be an integral part of dealing with this problem.

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Alternate therapies

Recommendation:

- Clinicians trained in modern system of medicine are advised not to prescribe alternate therapies to treat diabetes.

Ayurveda, Yoga, Unani, Siddha, Homeopathy and Naturopathy systems of Medicine are often integrated into diabetes health care delivery. More than 300 Indian plant and mineral products have been reported, with sub-optimal therapeutic effects in diabetes. Multi-center, randomized clinical trials, have established a few beneficial effects of Methi, Vijaysar, Amla, Turmeric and Karela in diabetes [1-6]. Yoga, Pranayama, meditations and many relaxation techniques are being practiced in India, for prevention and management of diabetes [7,8]. Although they do not substitute physical activity, they may supplement non-pharmacologic therapies in diabetes.

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Individualizing therapy

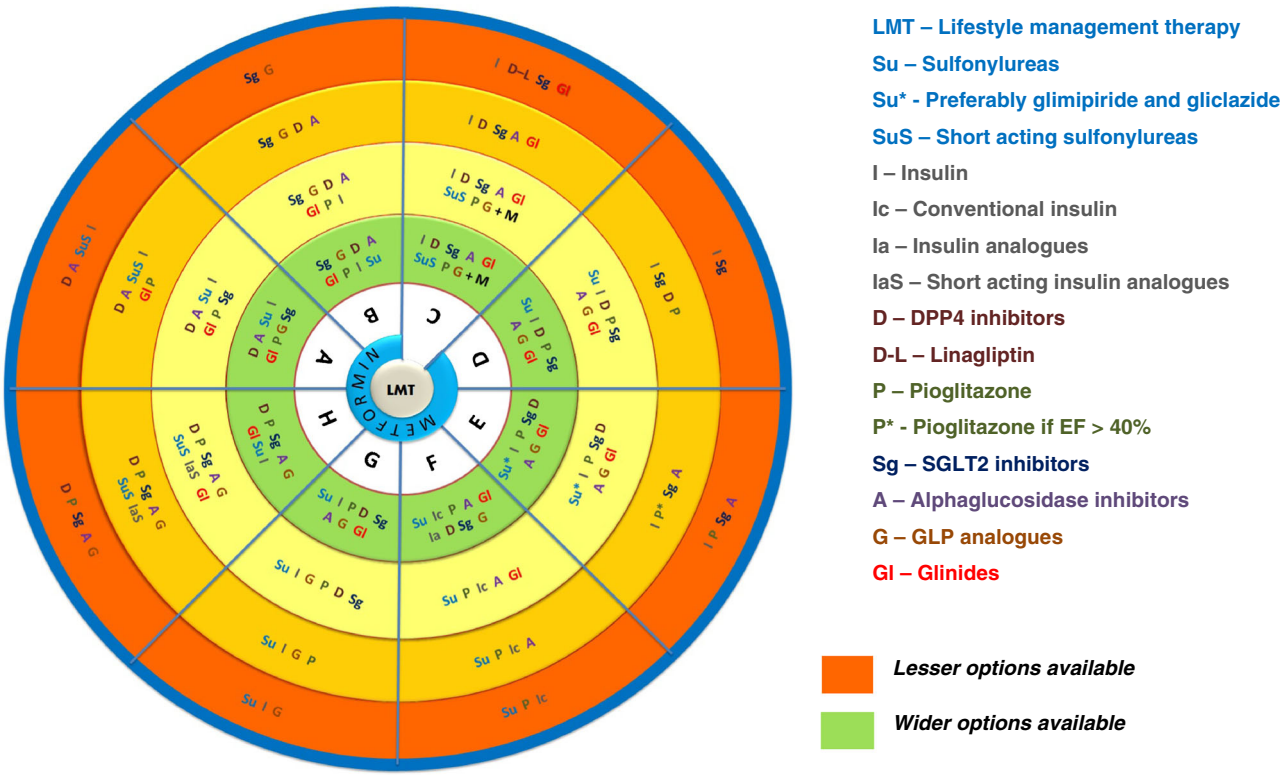
RSSDI 2015 recommendations

ABCD (EFGH) approach for diabetes management

Choice of any anti-diabetic agent should take into account the patient's general health status and associated medical disorders. This patient centric approach may be referred to as the ABCD (EFGH) approach for diabetes management. As shown in the figure, for any T2DM patient first line of therapy should be Metformin unless not tolerated or contraindicated.

Individualized treatment

- For a patients who has been diagnosed with diabetes consider a combination of metformin and one of these treatment options based on Patients **A**ge, **B**MI, **CKD**, **D**uration of Diabetes**, E**stablished CVD, **F**inancial concern, **G**lycemic status and Hypoglycemia concern.
- Drug choice should be based on patient preferences as well as presence of various comorbidities and complications, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia and weight gain.
- A comparative effectiveness meta-analysis[1] suggests that overall each new class of noninsulin agents added to initial therapy lowers HbA1c around 0.9–1.1% [1].



From Innermost to Outermost : A → Age = Advancing Age; B → BMI = Increasing BMI; C → CKD = Advancing CKD; D → Duration of Diabetes = Increasing Duration; E → Established CVD = Low CVD risk to Established CVD Risk; F → Finance = Adequate to Limited; G → Glycemic Status = Worsening glycemic control; H → Hypoglycemia = Hypoglycemia concern

Age

- eGFR adjusted doses of gliptins may be a suitable addition to metformin for elderly patients in whom one will like to avoid hypoglycemia and weight gain [2].
- Agents belonging to AGI could also be important choice in elderly patient. These agents have moderate efficacy but minimal side effects.
- In elderly males, glitazones may be a safer alternative in patients with preserved cardiac function. However, post-menopausal females must be spared for its use because of high predisposition to osteoporosis.
- While SU's, GLP-1RA, SGLT-2 inhibitors or Glinides should emerge as last choice since there are adverse effects as well as premium price associated with these agents. Risk benefits ratio must be properly evaluated before using them.

BMI

- GLP-1 RA seems to be the best add on therapy for those having high BMI. This group of medications have highest weight reducing property in addition to the excellent efficacy
- SGLT-2 inhibitors also have a weight reduction property. The medicines in this group have an additional advantage of excellent tolerance and can be given orally as compared to GLP-1 RA. However their glycemic efficacy seems to be less than that of GLP-1 RA. The experience with this group of agents is less than that with GLP-1 RA [3].
- AGI's and Gliptins are weight neutral and so can be used as third line of agents.
- The last option for such kind of patients should be SU's, Insulin or Glitazones since they are having weight gain properties.

CKD

- In the same manner if we focus on complications (renal impairment) preference of therapy would be Gliptins as add on therapy with metformin [4]. Few of the gliptins need dose adjustment as per eGFR while Vildagliptin needs dose adjustment in hepatic insufficiency. Linagliptin does not require any dose adjustment in renal disease.
- Repaglinide is another agent which may be used across all stages of renal insufficiency. Similarly glitazones may be used in CKD, however, one has to careful about fluid retention.
- Short acting sulfonylureas Glipizide and Gliclazide may also be used across renal insufficiency, however hypoglycemia is a huge limiting factor. AGIs may be used in patients with mild to moderate renal disease.
- Insulin may be used in any stages of renal insufficiency and is the best agent for this purpose.

Duration of diabetes

- As results of recent trials have suggested to utilize an aggressive approach in cases where duration of diabetes is less than 5 years, SU or glinide, as an add on therapy to metformin, will be the best choices, being very potent agents. Addition of glitazones may be useful at this stage [5].
- GLP-1 RA may score over gliptins for this indication as they are more efficacious than gliptins.Gliptins may be an option for 2nd add on agent.
- SGLT-2 inhibitors may also be useful as second add on agent due to their insulin independent action which is patho physiologically different.
- AGI's are last choices due to their moderate efficacy.

Established CVD

- In patients with established CVD, DPP-4 inhibitors may be preferred agents after Pioglitazone, SGLT-2 inhibitors and AGIs because of low risk of hypoglycaemia. GLP-1 analgoues may be a suitable alternative for patients who are overweight or obese. AGIs may be preferred in patients with postprandial hyperglycaemia.
- Pioglitazone has also been shown in different studies to reduce CVD risk.
- Recent data from EMPA-REG study has shown that SGLT inhibitors reduce CV risk and CV mortality, and may be preferred.

Financial concern

- Cost of therapy also plays an essential role considering that treatment needs to be continued lifelong.
- SUs should be first choice with metformin by considering its cost, then after AGI's or Glitazone should be used at next therapy level [6], in the next level the therapeutic option should be Glinides or Insulin.
- High cost will prevent the use of insulin analogues, Gliptins, SGLT-2 inhibitors and GLP-1 RA in most of the patients [7].

Glycemic status

- Good glycemic control of patients is directly correlated with efficacy of any anti-diabetic agent.
- Insulin followed by GLP-1RA, SUs and glitazones have highest efficacy in terms of reducing HbA1c [8].
- Gliptins, SGLT2 inhibitors or AGIs should be considered as add on therapy if these agents are not able to achieve glycemic targets.
- It is always to be understood that good efficacy, in most cases, come with a price written on it in the form of increased incidence of hypoglycemia or prohibitive cost.

Hypoglycemia concern

- Hypoglycemia is the biggest hurdle that any medical fraternity is facing during treatment course of diabetes.
- In patients with history of hypoglycemia or for those at high risk of hypoglycemia, GLP-1RA or gliptins should be considered as first choice with [9]. Other options include SGLT-2 inhibitors, glitazones, and AGIs.
- Last option for such patients should be either Glinides, SU's or Insulin since there are high chances of hypoglycemia with these agents.
- Group of patients where one will require avoiding hypoglycemia include:
  - those with established CV disease
  - elderly patients
  - those suffering from retinopathy and cannot perform SMBG without help of others
  - those who stay alone, especially in remote areas
  - those who are having poor longevity
  - those who are having documented hypoglycemia unawareness
  - those who met with severe symptomatic hypoglycemia requiring hospitalization

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Postprandial hyperglycemia

RSSDI 2015 recommendations

Recommended care

- Post-meal hyperglycemia (PPHG) is defined as a 2-hour plasma glucose level of more than 200 mg/dl during OGTT with 75g anhydrous glucose
- Post-meal hyperglycemia is harmful and should be addressed
- Treatment strategies to lower post-meal plasma glucose in people with post-meal hyperglycemia should be implemented
- Post-meal plasma glucose should be measured 1-2 hours after a meal.

  - The target for post-meal glucose is 160 mg/dl as long as hypoglycemia is avoided

- A variety of both non-pharmacologic and pharmacologic therapies should be considered to target post-meal plasma glucose

  - Medical Nutrition Therapy that includes diet with low glycemic load is recommended in all patients with PPHG
  - Pharmacological agents to lower PPHG include:

    - Alpha glucosidase inhibitor (acarbose or voglibose), DPP-4 inhibitors, or GLP-1 analogues are recommended as a first line therapy for treatment of PPHG
    - Glinides and short acting sulfonylureas are recommended as second line agents to control PPHG
    - Rapid acting insulin analogues should be preferred over the regular insulin when PPHG is a concern
    - Combination therapy of AGI with other agents may be considered for better control of PPHG
    - Self-monitoring of blood glucose (SMBG) should be considered because it is currently the most practical method for monitoring post-meal glycemia

Limited care

- The principles for management of PPHG are as for Recommended care

Preamble

Poorly controlled diabetes is associated with increased risk of micro- and macro-vascular complications which further depend upon both fasting and postprandial glucose levels [1,2]. Evidence from large controlled clinical trials suggests that intensive glycemic control can significantly decrease the development and/or progression of these complications [3-6]. However, tight glycemic control needs to be instituted early in the disease course and the benefit may take many years to manifest. The relationship between hyperglycemia and CVD is complex with evidence suggesting that an acute increase of glycemia, particularly after a meal, contributes to the increased risk of diabetes-related complications and have a direct detrimental effect on CVD in patients with T2DM [7,8]. Until recently, the predominant focus of diabetes treatment has been on lowering HbA1c levels, with emphasis on FPG [9]. Nevertheless, control of fasting hyperglycemia alone is insufficient to obtain optimal glycemic control. Emerging evidence suggests that reducing post-meal plasma glucose excursions is as important, or perhaps more important for achieving desired glycemic targets [10]. Therefore targeting both PPG and FPG is an important strategy for achieving optimal glycemic control. The purpose of these recommendations are to assist clinicians in developing strategies to consider and effectively manage post-meal glucose in people with T2DM in Asian countries.

Considerations

India has a high prevalence of diabetes and onset of diabetes is a decade early. Post meal hyperglycemia is more prominent in Indians due to high traditional diets with high glycemic index. Literature is limited regarding post meal hyperglycemia despite a definite role in micro and macrovascular complications.

Rationale and evidence

Definition of PPHG

- American Diabetes Association (ADA) 2013 defines post-meal hyperglycemia as a 2-hour plasma glucose level of more than 200 mg/dl during an OGTT. It recommends the use of a glucose load equivalent of 75 g anhydrous glucose dissolved in water as prescribed by WHO. On the other hand, IDF 2011, defines PPHG as a plasma glucose level of 140 mg/dl or more, after 1-2 hours of food [11,12].
- Asian Indians display marked rise in prandial glucose excursion after consumption of 75 gm of bread meal compared to Caucasian counterparts [13].

PPHG is harmful

- Elevations in post meal plasma glucose are due to the loss of first phase insulin secretion, decreased insulin sensitivity in peripheral tissues, and consequent decreased suppression of hepatic glucose output after meals due to insulin deficiency [14].
- The panel suggested that PPHG is an independent risk factor for the development of several complications including [15]:

  - Macro-vascular disease
  - retinopathy
  - cancer
  - impaired cognitive function in elderly people with T2DM
  - increased carotid intima-media thickness
  - decreased myocardial blood volume and myocardial blood flow
  - oxidative stress, inflammation and endothelial dysfunction

- Evidence from an Indian study in subjects with a history of T2DM for more than 25 years, suggests that PPHG was associated with increased risk of both diabetic nephropathy and neuropathy [16].
- The causes of PPHG are influenced by many factors which include a rapid flux of glucose from the gut, impaired insulin release, endogenous glucose production by the liver and peripheral insulin resistance [8].

Addressing PPHG

- Currently there is lack of data linking improved clinical outcomes with that of correcting PPHG. Neither the HEART2D study nor the NAVIGATOR study could demonstrate direct benefit of lowering PPHG in reducing CVD in patients with T2DM [17-19].
- However, emerging evidence indicates that agents which target post meal plasma glucose show significant positive trends in risk reduction for all selected cardiovascular events. Findings from the STOP-NIDDM trial also showed that treating people with IGT with acarbose is associated with a significant reduction in the risk of CVD and hypertension [20]. Therefore the panel opined that addressing PPHG is as important with a recommended target of 160 mg/dl as long as hypoglycemia is avoided.
- PPHG is an important pathophysiological state contributing to the pathogenesis of CVD in people with and without diabetes. PPG should be routinely monitored in T2DM patients. Serum glucose level 2 h post-OGTT must be performed as it is a powerful predictor of all-cause premature death and CV risk, and a better indicator than FPG [21,22]. Management of PPHG is central to long-term glycemic control and an essential part of CVD prevention in IGT and T2DM. The level of implementation of routine screening for PPHG, using the OGTT, should be improved in the Asia-Pacific region, combined with wider use of effective interventions to manage PPHG [23].

Strategies to prevent PPHG

Non-pharmacological

- Traditional Asian Indian and Chinese diets are carbohydrate-rich (as high as 80% of the macronutrient composition) with high glycemic index values [24]. The higher carbohydrate load in the Indian diet leads to greater prandial glycemic excursion, increased glucosidase and incretin activity in the gut which leads to higher lipemic peaks and associated cardiovascular disease [24]. Evidence suggests that diet with low glycemic index values are beneficial in controlling PPHG [25,26].
- To promote effective PPHG control, the panel emphasized on advising patients on Medical Nutrition Therapy (MNT) which should include:
  - Carbohydrate should constitute 45-65% of total caloric intake, with a minimum of 130 g/day for adults
  - Consumption of low glycemic index foods
  - Increase intake of soluble and insoluble fiber
  - Consumption of fruits and vegetables in place of refined carbohydrate

Pharmacological

- Based on limited Indian evidence available from literature, the panel relied on expert opinion for pharmacological management of PPHG which includes the following:
  - Therapies which have been available for some time include α-glucosidase inhibitors (acarbose and voglibose), glinides (rapid-acting insulin secretagogues), short-acting sulfonylureas (glipizide) and insulins (rapid-acting human insulins/insulin analogues and biphasic [premixed] human insulins/ insulin analogues).
  - In addition, new classes of therapies for managing PPHG such as GLP-1 derivatives (exenatide and liraglutide) and DPP-4 inhibitors have shown significant benefits in reducing post meal plasma glucose excursions and lowering HbA1c.
  - Metformin should remain the first-line of therapy, unless specifically contraindicated, in view of its benefits and its relatively benign side-effect profile in most cases of T2DM irrespective of its effect on PPHG.
  - Use of glinides is limited to the treatment of PPHG only if sulfonylureas are contraindicated or in patients who cannot afford or are not otherwise candidates for the newer agents.
  - AGIs (acarbose, miglitol and voglibose) can be used as first-line drug in early T2DM, as well as in combination with nearly all established oral antidiabetic and insulin. AGIs have been shown to effectively control PPHG while providing additional benefits in terms of cardiovascular risk protection [27,28]. Moreover, AGIs tend to inhibit carbohydrate absorption from gut which can be of particular importance in Indian settings where there is increased odds for post-meal glycemic and lipid excursion due to consumption of diets with high glycemic index.

Implementation

Frequent monitoring of glucose levels using techniques such as self-monitoring of blood glucose (SMBG) can significantly

improve glycemic control besides detecting postprandial excursion. SMBG is currently the optimal method for assessing plasma glucose levels. Evidence suggests that structured SMBG followed by therapeutic interventions results in greater HbA1c reduction in people with T2DM compared with programs without structured SMBG [29-31]. Therefore the panel opined that SMBG with appropriate patient education is necessary for optimal management of PPHG.

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Clinical monitoring

RSSDI 2015 recommendations

Recommended care

- Monitor blood glucose control by measuring HbA1c using high-precision methods standardized to criteria aligned to the international reference values and subject to stringent quality assurance testing when no conditions are present in a patient that would preclude its accurate measurement
- Measure HbA1c every 2 to 6 months depending on level, stability of blood glucose control and changes in therapy
- Report HbA1c results in %
- Provide HbA1c result, in the laboratory, before the clinical consultation
- Anaemia and abnormal hemoglobin may affect the values obtained for HbA1c in some assays. To determine whether abnormal hemoglobin are present, use high-performance liquid chromatography (HPLC) or mass spectrometry
- Estimated average glucose ([eAG] reported in either mmol/l or mg/dl) is derived from HbA1c. Only a few countries have chosen to report eAG due to its limitations and lack of applicability to all ethnic groups. It may help people with diabetes relate their HbA1c to daily glucose monitoring levels or highlight when HbA1c is inappropriate.
- Measure blood glucose when patients are hospitalized, either at site-of-care or in the laboratory. Site-of-care capillary blood glucose meters should be monitored by certified quality assurance schemes. Ascertain whether meters are calibrated against plasma or blood

Limited care

- If HbA1c measurement is not available, blood glucose could be used for clinical monitoring measured either at site-of-care or in the laboratory
- Site-of-care capillary blood glucose meters should be quality controlled by certified quality assurance schemes or by reference to laboratory methods

Targets of glucose control

Recommended care

- Advise people with diabetes that maintaining an HbA1c below 7.0% minimizes the risk of developing complications
- A lower HbA1c target may be considered if it is easily and safely achieved
- A higher HbA1c target may be considered for people with co-morbidities or when previous attempts to optimize control have been associated with unacceptable hypoglycemia
- An individual's HbA1c target should be regularly reviewed taking into account benefits, safety and tolerability

- Treatment should be reviewed and modified if HbA1c level is above the agreed target on two consecutive occasions
- Advice those in whom target HbA1c levels cannot be reached that any improvement is beneficial
- Target values for glucose control for HbA1c and capillary plasma glucose are as follows:

	Normal	Target
HbA1c	< 6.0 % / 42 mmol/mol	< 7.0 % / 53 mmol/mol
FPG	5.5 mmol/l (100 mg/dl)	6.5 mmol/l (115 mg/dl)
PPG	7.8 mmol/l (140 mg/dl)	9.0 mmol/l (160 mg/dl)

Limited care

- The principles are as for *recommended* care including assessment of diabetes control by HbA1c measurement. In very limited settings diabetes control may need to be based on measurement of plasma glucose levels alone.

Other clinical monitoring

Type of monitoring	Recommended care	Limited care
Complete history and physical examination	• A complete history and physical examination is recommended • Periodicity : Annually	• As for recommended care
Ophthalmic	• Detailed exam by qualified ophthalmologist • Dilated • Periodicity : At diagnosis and every two years if there is no retinopathy	• If ophthalmologists are not available need to adapt low cost technology to enable GPs to learn and use fundus photography
Smoking Cessation	• If present counselling by physician at every visit	• As for recommended care
BP measurement	• BP measurement at each visit	• As for recommended care
Measurement of lipids	• At diagnosis or at 40 and periodically (6monthly) thereafter	• At diagnosis or at 40 at least
Screening for cardiovascular disease	• Not recommended	• As for recommended care
Microalbuminuria	• At diagnosis and annually thereafter	• If resources are limited and technical issues may consider use of ACEI/ARB if BP is > 140/80
Distal peripheral neuropathy	• At diagnosis and at least annually • Test for vibration with 128 hz tuning fork or a 10g monofilament, pinprick sensation ankle jerk	• As recommended by IDF • Additional training required
Peripheral arterial disease	• At diagnosis • History of claudication, distal pulses and ABI	• As for recommended care • Additional training required
Comprehensive foot care	• At diagnosis and annually • Assessment of foot pulses, and testing for loss of protective sensation (10-g monofilament plus testing any one of: vibration using 128-Hz tuning fork, pin-prick sensation, ankle reflexes, or vibration perception threshold	• As for recommended care • Additional training required

Preamble

Monitoring of blood glucose levels is critically important to ensure good glycemic control. It is considered the corner stone of diabetes care that helps both physicians and patients to adjust the therapy according to patient's need. Following clinical testing to assess levels of control and progression of T2DM, most guidelines recommend clinicians to perform frequent monitoring of glycemic status by measurement of HbA1c as a follow-up care of individuals with diabetes [1]. Measuring HbA1c is gold standard for the therapeutic management of diabetes in both research and in clinical settings, which involves assessing glycemic control over the previous 2–3 months [2]. Long-term hyperglycemic as measured by HbA1c have been shown to be strongly related to development of diabetic micro-vascular complications though its relation to development of macro-vascular complications is less clear. Therefore patients who are not at targets or at increased risk of developing complications require more intensive monitoring, ranging from frequent self-monitored glucose [3] to continuous glucose monitoring [4] to assess daily variations in blood glucose levels [5]. The current recommendations provides an insight on the importance and frequency of monitoring to be performed in order to facilitate medication and lifestyle changes when average HbA1c values remain above targets levels.

Considerations

The decision on monitoring of glycemic levels T2DM patients was based on the local factors such as availability of newer

technologies and cost of monitoring that were reviewed in Indian context.

Rationale and evidence

HbA1c for monitoring blood glucose

- Several guidelines and literature pertaining to monitoring emphasize on adjustments to the treatment based on glycemic measurements, methods available for monitoring and their quality implementation. Evidence suggests that that regular monitoring of HbA1c will facilitate identification of patients with poor glycemic control and help both physicians and patients to take necessary steps to achieve desired glycemic targets [6]. Though frequent monitoring of HbA1c is associated with reduced diabetes-related complications and improved metabolic control [7], most patients do not understand or are not aware of importance of glycemic monitoring. Therefore it becomes absolutely necessary to empower the patients with knowledge and understanding on HbA1c levels for optimal glycemic control that will in turn motivate them to effectively manage their diabetes [8].
- The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Working Group on HbA1c Standardization has established a reference measurement procedure (HPLC-MS or HPLC-CE) for HbA1c embracing the concept of metrological traceability [9].
- Though IDF recommends reporting IFCC units (mmol HbA1c per mol unglycated hemoglobin), the panel suggested reporting HbA1c in DCCT aligned values (%) as majority of the physicians are not familiar with new IFCC units. However, it was emphasized that the healthcare professionals should be made aware of the new IFCC units and encouraged to practice them during routine clinical practice.
- The concept of estimated average glucose (eAG) was introduced following introduction of continuous ambulatory blood glucose monitoring [10]. eAG may help people with diabetes relate their HbA1c to daily glucose monitoring and highlight any inaccuracies in HbA1c measurement relative to glucose levels [11]. There now calculators available for converting HbA1c to eAG in both mmol/l and mg/dl. Measurement of timed glucose levels are often recommended as a substitute for HbA1c when the latter is either unavailable or inappropriate.
- Abnormal hemoglobin levels are known to affect HbA1c values in a way that can significantly alter the results with regard to diabetes control [12]. Therefore it is important to consider hematological factors that can confound HbA1c levels in people with diabetes, best detected using HPLC-based assays.
- Measurement of blood glucose using blood glucose meters on admission to hospital wards helps to identify patients with hypoglycemia or hyperglycemia. Considering that in developing nations like India, where cost is major barrier for monitoring, these devices should be accurate, cost effective and field tested specifically tailored for Asian and Indian needs is imperative. Such data is available from only one study in India by Dr. Mohan's group from Chennai that evaluated the performance of glucose meter for Indian conditions across different values and temperatures [13].

Glucose measurement

- Plasma glucose is the preferred measure of most modern laboratories. Whole blood gives lower readings due to the volume occupied by hemoglobin. Capillary blood glucose strips measure the glucose in the plasma of the capillary blood sample, but may be calibrated to give results either as plasma or sometimes whole blood glucose (check meter instructions).

Implementation

There should be access to a laboratory or site-of-care test monitored by certified quality assurance schemes for measurement of HbA1c. People in whom HbA1c measurement is inappropriate must be identified by careful review of hematological parameters and other factors that can affect HbA1c values. Provision of capillary blood glucose meters and strips needs to be assured in hospitals and clinics. It is important to ascertain whether there are contraindications for use of a meter in a particular patient. It is essential to establish whether meters report values for plasma or blood and to ensure that schemes for monitoring the quality of their output are in place. Blood glucose meters should be calibrated on regular basis and their use in hospitals should be restricted to trained personnel.

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Self-monitoring of blood glucose

RSSDI 2015 recommendations

Recommended care

- Self-monitoring of blood glucose (SMBG) should only be made available to people with diabetes who have the required knowledge, skills and willingness to use the information obtained through testing to actively adjust treatment, enhance understanding of diabetes and assess the effectiveness of the management plan on glycemic control
- The purpose(s) of performing SMBG and using SMBG data should be agreed between the person with diabetes and the health-care provider
- SMBG on an ongoing basis should be available to those people with diabetes using insulin
- SMBG protocols (intensity and frequency) should be individualized to address each individual's specific educational/behavioral/clinical requirements/specific needs and goals (to identify/prevent/manage acute hyper- and hypoglycemia) and provider requirements for data on glycemic patterns and to monitor impact of therapeutic decision-making
- Intensive/regular SMBG may be recommended if a person with diabetes is on multiple daily insulin injections, pregestational diabetes on insulin, history of hypoglycemia unawareness, have brittle diabetes or with poor metabolic control on multiple OADs and/or basal insulin. SMBG should be performed at least as often as insulin is administered:
  - For patients on intensive insulin regimens who are on multiple doses of insulin or on insulin pumps should be tested three or more times daily (all pre-meals, post-meals, bedtime, prior to exercise)
- SMBG plays important role when a patient suspect low blood glucose or after treating low blood glucose until they are normo-glycemic, and prior to critical tasks such as driving. For many patients, this will require testing 6–10 (or more) times daily, although individual needs may vary. Similar considerations apply for pregnant women on insulin
  - Pregnant women with insulin-treated diabetes should be advised to perform SMBG on a daily basis, failing which, at least weekly monitoring should be encouraged
  - Ideal SMBG: 7 tests/day i.e. 3 before and 3 after each meal and 1 test at 3 am. As a compromise 1 fasting and 3 each after breakfast, lunch and dinner daily may be more feasible and acceptable, which can further be individualized to twice or thrice a week as the pregnancy advances. Two hour post meal monitoring may be easier to remember as this timing is routinely used
- In accordance with the sick day rule, the frequency of SMBG should be increased in special situations like fever, vomiting and persistent polyuria with uncontrolled blood glucose, especially if abdominal pain or rapid breathing is present. Ketone test should be performed as and when needed

- SMBG accuracy is instrument and user dependent, so it is important to evaluate each patient's monitoring technique, both initially and at regular intervals thereafter. The ongoing need for and frequency of SMBG should be re-evaluated at each routine visit
- SMBG should be considered for people using oral glucose lowering medications as an optional component of self-management, and in association with HbA1c testing:
  - To provide information on, and help avoid, hypoglycemia
  - To assess changes in blood glucose control due to medications and lifestyle changes
  - To monitor the effects of foods on postprandial glycemia
  - To monitor changes in blood glucose levels during intercurrent illness
- SMBG may be useful in T2DM, during periods of acute illness; using sulphonylurea or glinides as combination or monotherapy; to identify hypoglycemia especially in the first 3 months of starting sulphonylurea; in those who experience episodes of hypoglycemia and those who have reduced awareness of hypoglycemia; are drivers and those who fast; under preconception care
- Regular use of SMBG should not be considered part of routine care where diabetes is well controlled by nutrition therapy or oral medications alone
- Structured assessment of self-monitoring skills, the quality and use made of the results obtained, and of the equipment used, should be made annually

Limited care

- SMBG using meters with strips, or visually read blood glucose strips, should be considered for people with diabetes using insulin

Preamble

Self-Monitoring of Blood Glucose (SMBG) has been well studied among individuals with diabetes and has proved to be useful tool in improving glycemic control. SMBG coupled with training in self-titration of insulin doses, has resulted not only in better compliance and glycemic control but good chances of achieving HbA1c target. The self-monitoring and self-titration by patients with diabetes remains only means to achieve targeted glycemic control. Landmark clinical trials of insulin treated patients have included SMBG as part of the multifactorial interventions to demonstrate the benefit of intensive glycemic control on diabetes complications[1,2]. SMBG is therefore an integral component of effective therapy which allows patients to evaluate their individual response to therapy and assess whether glycemic targets are being achieved. The benefits of integrating SMBG results into diabetes management can be immense and can be a useful tool for guiding medical nutrition therapy and physical activity, preventing hypoglycemia, and adjusting medications (especially prandial insulin doses). Clinical evidence supports a correlation between greater SMBG frequency and lower HbA1c .The patient's specific needs and goals should not only determine but in fact should dictate SMBG frequency and timing [3].

Despite being recommended in various guidelines [3,4], a large gap between recommended to current practices of SMBG is observed in both developed and developing countries. In India, this strategy is still not properly understood or implemented. Lunch and dinner are our major meals of the day and glycemic variation are not recorded during routine tests which are invariably done in the morning. Availability of meals with varying glycemic indices and affordability of glucose meters and strips are major factors that play a dominant role either in recommending or practicing SMBG. Fortunately, the advent of less expensive meters and a reduction in the cost of the strips has considerably brightened the scenario. In this consensus, we have evaluated various literatures and guidelines on SMBG available online and drawn statement to fit Indian scenario.

Considerations

The decision including SMBG in clinical practice was based on the factors such as availability of and access to glucose meters and foods with varying glycemic indices that were reviewed in Indian context.

Rationale

The aims of SMBG should include the following: [5,6]

- Accurately assess level of metabolic control by individual therapy
- Achievement of realistic targets
- Prevention of both acute and chronic complications of diabetes.
- Reduce the effect of extreme glycemic excursions on cognitive function
- Assure proper data collection in various diabetes centers in order to provide an opportunity of comparison
- Enhance and enable improvement in interdisciplinary care for patients with diabetes
- Benefits can be achieved by maintaining proper record either in a form of a diary or electronic record keeping
- Record keeping should incorporate blood glucose readings, insulin dosage, record of special circumstances like

illness, eating out, exercise, any episode of hypoglycemia and its severity and any episode of ketonuria or ketonemia
- SMBG requires an easy procedure for patients to regularly monitor the performance and accuracy of their glucose meter

Optimization

SMBG accuracy is dependent on the instrument and user so it is important to evaluate individual patient's monitoring technique, both initially and at regular intervals thereafter. Optimal use of SMBG requires proper review and interpretation of the data, both by the patient and health care provider [7]. Among patients who check their blood glucose at least once daily, many report taking no action when results are high or low. Patients should be taught how to use SMBG data to adjust food intake, exercise, or pharmacological therapy to achieve specific goals. The ongoing need for and frequency of SMBG should be re-evaluated at each routine visit. SMBG is especially important for insulin-treated patients to monitor for and prevent asymptomatic hypoglycemia and hyperglycemia [8].

Evidence from India

- In a study by Shaji et al, that assessed knowledge, attitude and practice of T2DM patients towards self-monitoring and the impact of SMBG on glycemic control reported that patients who monitored ≥3 times had significantly better glycemic control of HbA1c (7.1–8 %) than those who monitor <3 times (p=0.021) [9].
- Selecting a structured, flexible SMBG pattern that can be tailored to the clinical, educational, behavioral, and financial requirements of individuals with diabetes is recommended. As it is important to determine the frequency and intensity of SMBG needed to support the chosen treatment regimen, one should also consider practical obstacles to monitoring, such as affordability or access and individualize glycemic target and modify monitoring patterns accordingly [5,10].
- Insulin self-titration interventions based on structured SMBG was associated with significant reduction in HbA1c during a follow-up of 12 weeks with a trend towards greater effectiveness in improving glycemic control than conventional treatment, with no increase in incidence of hypoglycemia or body weight gain [11].

Implementation

It is essential to establish whether meters report values for plasma or blood and to ensure that schemes for monitoring the quality of their output are in place. Blood glucose meters should be calibrated on regular basis. Low cost glucose strips and meters should be developed and made available for wider implementation of SMBG. Strategies that can lower post-meal glycemic excursions in people with PPHG should be implemented.

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Chronic complications

RSSDI 2015 recommendations for diabetic retinopathy

Recommended care

- Ensure that examination of the eyes of people with type 2 diabetes is performed around the time of diagnosis and then routinely every 1-2 years as part of a formal recall process:
  - Measure and document visual acuity, corrected with glasses or pinhole.
  - Assess retinopathy:
    - Using retinal photography through dilated pupils, performed by an appropriately trained health-care professional, or
    - By examination by an ophthalmic specialist
- Discuss the reasons for eye examination with the person with diabetes
- Counsel women who are planning pregnancy on the risk of progression of retinopathy during pregnancy especially if there is pre-existing retinopathy. Ensure regular follow up throughout pregnancy and up to one year post-partum
- Use tropicamide to dilate pupils, unless contraindicated, after discussing the implications and obtaining agreement of the person with diabetes
- Classify the findings of eye examination as requiring: routine review, earlier review or referral to an ophthalmologist (if not making the examination)
- The following frequency of screening is suggested:
  - 1-2 years if no retinopathy
  - 12 months if minimal unchanged retinopathy
  - 3 to 6 months if worsening since last examination
  - More often during pregnancy
- The following situations require specialist referral:
  - The same day:
    - Sudden loss of vision
    - Evidence of retinal detachment
  - Within 1 week:
    - Evidence of pre-retinal and/or vitreous hemorrhage
    - New vessel formation or rubeosis iridis
  - Within 1-2 months:
    - Advanced retinal lesions (4:2:1 rule):
      - Microaneurysms or retinal hemorrhages in 4 quadrants.
      - Venous beading in 2 quadrants
      - IRMAs in 1 quadrant
    - Unexplained deterioration of visual acuity
    - Macular edema
    - Unexplained retinal findings
    - Cataract
    - Inability to visualize fundus
- Advice that good control of blood glucose, blood pressure and blood lipids can help to reduce the risk of development or worsening of eye complications
- Advice that diabetic retinopathy is not a contraindication for use of aspirin if this is indicated for prevention of CVD
- Advice that tests of intra-ocular pressure should be made periodically
- Explain guarded prognosis about regaining vision after IOL surgery in mature/hypermature cataract because of poor assessment of retina in the presence of mature cataract

Limited care

- Use direct fundoscopy through dilated pupils, performed by a member of the health-care team who is properly trained and has appropriate experience to assess retinopathy
- Check visual acuity
- Repeat review, referral and preventative therapy are as for Recommended care
- Less-frequent examinations (every 2 years) may be considered following one or more normal eye examinations

Preamble

Diabetic retinopathy (DR) is a microvascular complication of diabetes and one of the leading causes of blindness or vision impairment in India [1]. Visual loss from DR could be due to diabetic macular edema (DME) or proliferative diabetic retinopathy (PDR). Global data suggests that the overall prevalence was 34.6% for any DR, around 7% for both DME and

PDR and 10.2% with vision-threatening DR. Longer duration of diabetes and poorer glycemic and blood pressure control were found to be strongly associated with DR [2]. Moreover, the socioeconomic burden resulting from DR induced visual impairment or blindness, particularly in the working age group, is a serious concern [3]. Therefore it is high time to devise the means of managing DR and bring the problem under control. A line of evidences has shown that the blindness from diabetes is almost entirely preventable with early diagnosis, optimization of risk factors and timely photocoagulation where appropriate [4]. A systematic approach to health education and creating awareness among patients and various health personnel and matching it with appropriate screening and service delivery mechanisms will go a long way in preventing blindness due to DR. These recommendations will provide insights on the management of DR while promoting awareness and thus preventing vision impairment due to DR though cost-effective interventions.

Considerations

The recommendations on management of DR were taken from IDF 2014. However few of the IDF recommendations were modified based on the local factors such as limited resources, high prevalence of DR, lack of quality assurance in labs and availability of newer technologies and therapies for eye screening and treatment which were reviewed in Indian context.

Rationale/evidence

Counselling pregnant women

- The possible relationship between the DR and the perinatal outcome has been addressed in several studies previously [5,6]. Women with higher severity of DR were more likely to develop obstetric complications [7] and those with proliferative changes accounted for higher incidence of congenital malformations and/or fetal death [8].
- As pregnancy can induce progression of DR, the panel recommended pre-conception counselling for women, clearly explaining about the risk of progression of DR during pregnancy especially if they already have proliferative retinopathy. They should be advised on maintaining good glycemic control before and throughout pregnancy under the guidance of healthcare professional. In addition the panel emphasized on the need for close follow-up during pregnancy and up to one year post-partum and monitor for progression of DR and co-existing hypertension and renal disease, if any.

Guarded prognosis after IOL surgery

- Though surgical intervention are crucial for cataract management, most of the patients, particularly those with complicated cataracts, may not restore the vision. These patients eventually develop corneal decompensation, glaucoma and optic atrophy. Because the prognosis of retina is poor especially in the presence of mature cataract, the panel suggested that it is important to educate the patient about guarded prognosis for regaining vision after IOL surgery [9].

Frequency of screening

- Several guidelines emphasize on eye screening in T2DM, however it appears they are divided on the frequency of screening. Some recommend annual screening (NICE-UK) while others recommend screening every 1-2 years (Canadian- Canada, Australian-Australia and SIGN-Scotland).
- With regard to frequency of screening in limited care setting, the panel endorsed the ADA recommendation which suggests less-frequent examinations (every 2-3 years) following one or more normal eye examinations [10].

Evidence

Though evidence from past studies suggests that prevalence of DR is low in Indians compared to other ethnic groups, emerging data indicate significant increase in prevalence of retinopathy in diabetic South Asians compared to Caucasians [11]. Data from population-based the CURES indicate that the overall prevalence of DR in urban South Indian population was 17.6%, with higher prevalence among men than in women (21.3% vs. 14.6%; $p<0.0001$) and among subjects with proteinuria ($p=0.002$) [12]. Similarly the prevalence of DR in western India was found to be 33.9% [13]. Data from a recent population-based cross-sectional study suggests that 1 of 10 individuals in rural South India, above the age of 40 years, showed evidence of DR [14]. Duration of diabetes, HbA1c, male gender, macro-albuminuria and insulin therapy were found to be strongly associated with increased risk of DR among South Indians [15]. Moreover, the risk of nephropathy (OR: 5.3, $p<0.0001$) and neuropathy (OR: 2.9, $p<0.0001$) was significantly higher among T2DM patients with DR compared to those without DR [16]. After adjusting for age, gender, HbA1c, systolic blood pressure, serum triglycerides, and duration of diabetes, DR was significantly associated with nephropathy ($p=0.005$) than with neuropathy [16].

Implementation

Sufficient number of trained general ophthalmologists and general physicians is required to develop an integrated DR model that facilitates early detection and create awareness on DR. Medical camps should be conducted for screening of diabetes and diabetic retinopathy screening camps that will help to identify people at risk of sight-threatening diabetic retinopathy and initiate treatment including laser photocoagulation or vitreous surgery. Mobile vans with a fundus camera or other low cost tools that can be used in remote rural areas should also be explored. However successful implementation of program requires team approach, involving both administrative and voluntary organizations.

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RSSDI 2015 recommendations for diabetic neuropathy

Recommended care

- Diagnose sensorimotor nerve damage by history and examination (10 gm monofilament with or without temperature, non-traumatic pin-prick, vibration [128 Htz tuning fork], ankle reflexes), and/or simple quantitative testing (e.g. biothesiometer vibration perception). Use serum B12, thyroid function tests, creatinine/urea, alcohol abuse and medication history to exclude other causes

- Diabetic Neuropathy Symptom Score (NSS) and Neuropathy Disability Score (NDS) in type 2 diabetes population has been found to be a useful resource in evaluating diabetic sensorimotor polyneuropathy as an important bed side tool
- Diagnose symptomatic (painful) diabetic neuropathy by excluding other possible causes of the symptoms. Manage by stabilizing blood glucose control, and treatment with tricyclic antidepressants if simple analgesia is not successful. If a one month trial of tricyclic therapy is not successful, further treatment options include pregabalin/gabapentin and duloxetine, then tramadol and oxycodone. Further management normally requires referral to a pain control team. Be aware of the psychological impact of continuing symptoms, particularly if sleep is disturbed. Inpatients with diabetic neuropathy and co-morbid depression anxiety and sleep loss, duloxetine should be preferred
- Diagnose erectile dysfunction by history (including medication history), exclusion of endocrine conditions (measure prolactin and testosterone), and a trial of a phosphodiesterase type-5 (PDE5) inhibitor (where not contraindicated by nitrate therapy). Consider other approaches such as intra-urethral or intracavernosal drugs and sexual and relationship counselling, where PDE5 inhibitors fail or cannot be used.
- Diagnose gastroparesis by history, trial of a prokinetic drug (metoclopramide, domperidone) and if troublesome by gastric emptying studies
- Diagnose cardiovascular autonomic neuropathy by resting heart rate and heart rate response to provocation tests (lying-standing, Valsalva, deep breathing), and by lying and standing blood pressure. Advise anesthetists when relevant where this is present

Limited care

- Screen and diagnose sensorimotor nerve damage by history of symptoms, and sensory assessment by 10 g monofilament or tuning fork with/without non-traumatic disposable pin-prick
- NSS and NDS in type 2 diabetes population has been found to be a useful resource in evaluating diabetic sensorimotor polyneuropathy as an important bed side tool
- Manage symptomatic (painful) diabetic neuropathy by excluding other causes, stabilizing glycemic control, and treatment with tricyclic antidepressants if simple analgesia is not successful. Opiate analgesia may be necessary as locally available
- Assess erectile dysfunction by history and examination and consider possible contributions of other medication or disease

Preamble

Neuropathies are the most common complication of diabetes, affecting up to 50% of patients with T2DM. Metabolic disruptions in the peripheral nervous system (altered protein kinase C activity and increased polyol pathway activity) due to hyperglycemia plays a key role in the development of diabetic neuropathy (DN) [1]. The prevalence of DN in India is estimated to be approximately 20-25% [2]. The most common form of DN is the distal symmetrical polyneuropathy that involves both tibial and sural nerves [3]. The presence of neuropathy is associated with significant morbidity, including recurrent foot infection and ulcers; impotence in diabetic men, and sudden death in individuals with cardiovascular autonomic neuropathy. Neuropathic pain in diabetic patients is commonly encountered in clinical practice. Therefore timely screening and early detection ensures prevention of the progression of DN [4]. The present recommendations provide insights on the management aspects DN while exploring newer therapeutic options that have emerged in recent years.

Considerations

The panel endorsed the IDF 2014 recommendations for diagnosis and management of DN. However, few of the recommendations were modified based on local factors such as limited resources, need for specific enquiry that helps in clinical diagnosis of neuropathy, lack of quality assurance in labs and need for cost-effective diagnostic techniques which were reviewed in Indian context.

Rationale/evidence:

Detection of sensorimotor polyneuropathy

- Though nerve conduction studies are powerful tools for identifying cases of neuropathy [5], using NSS (Annexure IX) and NDS (Annexure X) in T2DM patients was found to be a useful resource in evaluating diabetic sensorimotor polyneuropathy as a bed side tool [6,7]. A cross sectional study in T2DM patients that examined the nerve conduction velocities of motor and sensory nerves, using NSS and NDS in patients of clinically detectable neuropathy patients showed significant electrophysiological changes with duration of disease [6]. Similar results were observed in other study where NNS and NDS together helped in prompt evaluation of the diabetic sensorimotor polyneuropathy also help in diagnosing subclinical cases [8]. A recent study that validated the use of NSS and NDS for clinical diagnosis of peripheral neuropathy in middle aged 855 T2DM patients showed that NSS and NDS can detect DN with a sensitivity of 71.1% & specificity of 90% and was found to be simple, acceptable, reproducible and validated method for early diagnosis of DN [7].

- The panel emphasized on neurological examination using NNS and NDS as it is important bed side tool and a useful resource in evaluating diabetic sensorimotor polyneuropathy.

Duloxetine in diabetic neuropathy

- Duloxetine is a selective inhibitor of reuptake of both 5-hydroxytryptamine and norepinephrine which, in 2004 was approved by US FDA for the treatment of painful diabetic neuropathy [9]. Results from randomized controlled clinical trials reveal that duloxetine provides significantly more diabetic neuropathic pain relief than either placebo or routine care with higher degree of safety and tolerability [10-12].

Implementation

Appropriate protocols should be developed for sensory testing and may include formal assessment using the NNS and NDS. Recommended medications should be available according to level of resources. Medical teams need to remain trained in the diverse manifestations of autonomic neuropathy.

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RSSDI 2015 recommendations for diabetic nephropathy

Recommended care

- Kidney function should be assessed at diagnosis and annually by:
  - Urine test for albuminuria
  - Measurement of serum creatinine and calculation of eGFR
- Urinary albumin: creatinine ratio (ACR) measurement in an early morning first void spot specimen is the preferred method for assessment of albuminuria/ proteinuria. Where a first void specimen is not possible or practical, a random spot urine specimen is acceptable. ACR can be measured in the laboratory or at site-of-care
- Control hyperglycemia, and avoid exercise before testing for albuminuria
- If ACR is raised (microalbuminuria), ACR > 25 mg/gm in men, > 35 mg/gm in women, repeat ACR twice over the following 4 months:
  - Microalbuminuria is confirmed if ACR is elevated in two out of three tests, in the absence of infection or overt proteinuria

  - If both repeat tests are not raised, check again annually
  - An ACR >300mg/gm indicates macro albuminuria

- Chronic kidney disease is diagnosed on the basis of a raised urine albumin/protein or a reduced eGFR (< 60 ml/min/1.73m^2) calculated from the MDRD formula and using a standardized creatinine assay
- Individuals with chronic kidney disease should be managed as follows:

  - Use ACE-inhibitors or ARBs in individuals with micro- or macro albuminuria, titrated to maximum tolerated dose
  - Intensify management of blood pressure (target ≤ 130/80 mmHg) using blood pressure lowering medications and dietary modification (low salt intake)
  - Intensify management of blood glucose
  - Monitor ACR, eGFR and serum potassium
  - Advice limiting protein intake to 1 g/kg daily if proteinuric but many Indian patients by itself may be taking only 0.6-0.8 g/kg/day. So protein restriction may be emphasized only to avoiding extra protein intake from non-vegetarian source
  - Intensify other renal and cardiovascular protection measures
  - Smoking leads to the progression of ESRD in diabetes so patients must be counselled for quitting smoking

- Agree referral criteria for specialist renal care between local diabetes specialists and nephrologists. Referral criteria might include eGFR <30 ml/ min/1.73m^2, progressive deterioration of kidney function, persistent proteinuria, biochemical or fluid retention problems or difficult diagnosis (To r/o non diabetic renal disease where fundus is normal and no proteinuria)

Limited care

- Check annually for proteinuria in an early morning urine sample (or a random sample) using a dipstick. If test is positive exclude urinary tract infection by microscopy (and culture if possible)
- Measure serum creatinine and calculate eGFR annually
- A simple inexpensive screening procedure for urinary protein excretion which can be used as a diagnostic test in OPD has been reported in Indian population. Estimated proteinuria (EPE) is useful in serial evaluation of Kidney function
- Manage those with proteinuria as follows:

  - If available consider use of angiotensin-II converting enzyme (ACE)-inhibitors or angiotensin receptor blockers (ARBs) taking into account cost.
  - Aim for blood pressure ≤ 130/80 mmHg using any blood pressure lowering medication and control of salt intake
  - Aim to achieve targets for blood glucose control
  - Aim to improve lipid profile using available medications
  - Check proteinuria status annually
  - Measure serum creatinine and calculate eGFR annually

Preamble

Diabetic nephropathy (DPN) is a leading cause of end stage renal disease (ESRD) affecting ~ 20-30% diabetics, is associated with increased cardiovascular mortality [1]. It affects 10 to 40 percent of T2DM patients who eventually suffer from kidney failure [2]. Cost of treatment of advanced chronic kidney disease (CKD) is substantial. Less than 10% of end stage renal disease (ESRD) patients have access to any kind of renal replacement therapy [3]. In a country with limited resources, it becomes appropriate to direct efforts toward prevention of CKD rather than the treatment. In India, with increase in the prevalence of diabetes, it becomes imperative to evolve definite guidelines for evaluation of diabetic nephropathy and suggest practical clinical recommendations to combat it. Improving glycemic control, aggressive antihypertensive treatment, and the use of ACE inhibitors or ARBs will slow down the rate of progression of nephropathy. In addition, protein restriction and other treatment modalities such as phosphate lowering may have benefits in selected patients.

Considerations

The panel endorsed the IDF 2014 recommendations for diagnosis and management of diabetic nephropathy. However, few of the recommendations were modified based on local factors such as limited resources, lack of quality assurance in labs, higher prevalence of diabetic kidney disease and hypertension and cost of treatment of kidney failure through dialysis or transplantation which were that were reviewed in Indian context.

Rationale/evidence:

Avoiding exercise before testing for albuminuria

- Screening of microalbuminuria and estimation of glycated albumin can help in the clinical management of diabetic nephropathy [4]. Screening for albuminuria by measuring urine albumin concentration or estimating albumin to creatinine (A/C) ratio are acceptable in Asian population [5]. However, evidence suggests that vigorous exercise even for short periods (15-20 min) leads to A/C ratios above the microalbuminuria threshold even in healthy subjects [6].
- Based on the evidences, the panel suggested that physicians should ask about recent vigorous exercise and avoid

measuring urine albumin excretion for at least 24 hr. in the presence of same.

Protein restriction

- IDF recommends limiting protein intake to 1 g/kg daily among individuals with CKD if they are found proteinuric. However from the Indian context, the source of protein in Indian diets is majorly from vegetable and animal oils and daily protein consumption is about 0.6-0.8 g/kg [7]. Protein content in non-vegetarian diet was found to be higher when compared to the vegetarian diet [8]. Therefore the panel emphasized on protein restriction, particularly in non-vegetarians with nephropathy, to avoiding extra protein intake.

Smoking

- Smoking is associated with hyperglycemia, dyslipidemia and decline in GFR which leads to the progression of ESRD in diabetes [9]. Smoking tends to induce albuminuria and abnormal renal function through formation of advanced glycated end products (AGE'S) which are responsible for advanced vascular permeability and kidney damage [10]. Data from a recent study in India suggests that compared to non-smokers the prevalence of microalbuminuria in smokers was 4-fold higher [11].
- The panel opined that patients must be counselled against tobacco use and encouraged to quit smoking to reduce the risk of progression to ESRD.

Referral to specialist

- The panel endorsed IDF recommendation on referral criteria, however it was suggested that, because most of the patients at this stage of diabetic nephropathy require a specialist care which may not be available at primary care or single physician center, local diabetes specialists should refer the patient to specialist renal care/nephrologist. Likewise, nephrologists should refer to patient to specialist renal care if the patient presents with following condition:
  - eGFR < 30 ml/min/1.73m^2
  - progressive deterioration of kidney function
  - persistent proteinuria, biochemical or fluid retention problems or
  - difficulty in diagnosis (To r/o non diabetic renal disease where fundus is normal and no proteinuria)

Screening for urinary protein excretion

- Estimated proteinuria (EPE) is a method of estimating protein to creatinine ratio (P/C ratio) in a random urine sample to assess renal function in diabetic patients. EPE was found to be useful in serial evaluation of kidney function Indian patients with diabetes [12]. Moreover EPE was a simple inexpensive screening procedure for urinary protein excretion which can be used as a diagnostic test in OPD particularly in developing countries like India.
- It being an inexpensive tool screening procedure to assess kidney function the panel recommended it for use in Indian population at risk of diabetic nephropathy.

Indian evidence

- Prevalence of microalbuminuria was strongly associated with age, diastolic blood pressure, glycated hemoglobin, fasting plasma glucose and duration of diabetes [13].
- A positive co-relation between urine albumin excretion rate and estimated glomerular filtration rate (eGFR < 60 ml/min/1.73m^2) was observed indicating that these two parameters provide a complimentary benefit in management of chronic kidney disorder [14].
- Vitamin D deficiency can have significant impact on albuminuria. Therefore supplementation with calcitriol should be considered in these patients as it has been shown to provide beneficial effects on microalbuminuria [15].

Implementation

Management of CKD requires access to healthcare professional, laboratory for ACR and creatinine estimations, and availability of multiple blood-pressure-lowering medications in particular renin-angiotensin system blockers.

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RSSDI 2015 recommendations for foot care

Recommended care

- Assess feet of people with diabetes as part of an annual review for lesions which require active treatment and for risk factors for ulcer and amputation:
  - History of previous foot ulceration or amputation, symptoms of peripheral arterial disease, physical or visual difficulty in self-foot-care
  - Foot deformity (hammer or clawed toes, bone prominences); visual evidence of neuropathy (dry skin, dilated veins) or incipient ischemia; callus; nail deformity or damage; footwear
  - Detection of neuropathy by 10 g Semmes Weinstein monofilament (or 128 Hz tuning fork); a biothesiometer (VPT) is an option for quantitative assessment (cut-off point for ulcer risk >25 volts); non-traumatic pin-prick
  - Palpation of foot pulses (dorsalis pedis and posterior tibial). Doppler or ankle:brachial pressure (ABI) ratio (< 0.9 for occlusive vascular disease) may be used where pulses are diminished to quantify the abnormality
- Discuss the reasons for foot review with each person with diabetes as part of the foot-care educational process
- Must emphasize not to walk bare foot at all including visit to religious places
- Timely screening and early detection of diabetic neuropathy may help in prevention of the progression to diabetic foot
- Agree a foot-care plan based on the findings of annual foot review with each person with diabetes. Assess and provide necessary foot-care education according to individual need and risks of ulcer and amputation
- Classify risk of ulcer or amputation according to findings of the foot assessment:
  - No added risk: no risk factors and no previous history of foot ulcer or amputation
  - At risk: one risk factor and no previous history of foot ulcer or amputation
  - High risk:
    - Two or more risk factors
    - Previous ulcer or amputation (very high risk)
    - Manage according to risk classification level:
  - **No added risk:** Provide foot-care education
  - **At risk:** Arrange regular review, approximately 6 monthly, by foot-care team
- At each review:
  - Inspect both feet – ensure provision of local management as indicated
  - Evaluate footwear – provide appropriate advice
  - Enhance foot-care education

– **High risk:**

  - Arrange frequent review every 3-6 months by foot care team
  - At each review:

    - Inspect both feet – ensure provision of local management as indicated
    - Evaluate footwear – provide advice and specialist insoles and shoes if indicated
    - Consider need for vascular assessment or referral if indicated
    - Evaluate and ensure the appropriate provision of intensified foot-care education

- People with foot ulceration or infection require the following management:

  – Pressure off loading
  – Refer to multidisciplinary foot-care team within 24 hours for:

    - Appropriate wound management, dressings and debridement as indicated
    - Infections should be classified as mild (superficial with minimal cellulitis), moderate (deeper than skin or more extensive cellulitis), or severe (accompanied by systemic signs of sepsis). Consideration of systemic antibiotic therapy (often longer term) for extensive cellulitis or bone infection as indicated; generic penicillin, cehalosporins, macrolides, clindamycin and/or metronidazole as indicated as first-line medications, with amino-quinolones, or co-amoxicillin as examples of second-line medications
    - Probing to bone, radiology and scans, magnetic resonance imaging, and biopsy where indicated for suspected osteomyelitis
    - Reduce weight bearing, relief of pressure (walking with crutches, rest) off loading and optimal pressure distribution (casting if indicated)
    - Investigation and treatment (referral) for vascular insufficiency
    - Specialist footwear and orthotic care (e.g. insoles), and individualized discussion of prevention of recurrence, when ulcer has healed
    - Optimal blood glucose control

  – Amputation should not be considered unless:

    - A detailed vascular evaluation has been performed by the vascular team
    - Ischemic rest pain cannot be managed by analgesia or revascularization
    - A life-threatening foot infection cannot be treated by other measures
    - A non-healing ulcer is accompanied by a higher burden of disease than would result from amputation

Limited care

- Risk assessment and classification would be as for Recommended care but with sensory assessment by 10 g monofilament or tuning fork, with or without non-traumatic disposable pin-prick only, and peripheral circulation assessment by palpation of pedal pulses
- NSS and NDS in type 2 diabetes population has been found to be a useful resource in evaluating diabetic sensorimotor polyneuropathy as important bed side tool
- Classification of infection would be as for Recommended care but antibiotic therapy would be with generic penicillin, quinolones, macrolides and/or metronidazole, given intravenously for deep tissue infections, and adjusted by response or culture results
- Vascular referral would be according to findings and local revascularization facilities

Preamble

Diabetic foot problems are one of the most common reasons for hospitalization of diabetic patients (about 30% of admissions) and consume about 20% of the total health-care costs of the disease compared to all other diabetic complications [1,2]. In India prevalence of foot ulcers in diabetic patients in clinic population varies from 3-14% [3,4]. Strategies aimed at preventing foot ulcers are cost-effective and can even be cost-saving if increased education and efforts are focused on those patients with recognized risk factors for the development of foot problem. The management of diabetic foot disease may seem poorly defined by comparison with complications such as nephropathy, hyperlipidemia and retinopathy, for which clear guidelines exist. A multidisciplinary team, approach, particularly in specialized diabetic foot clinics, is very successful in avoiding and treating foot complications. Present guideline focuses on the various mechanisms of managing diabetic foot disease.

Considerations

The panel endorsed the IDF 2014 recommendations for diagnosis and management of diabetic foot. However, few of the recommendations were modified based on local factors such as limited resources and lack of quality assurance in labs, which were reviewed in Indian context.

Rationale/evidence

Detection and timely screening of neuropathy

- Vibration perception threshold (VPT) is considered as a gold standard for diagnosis of diabetic peripheral

neuropathy. However, use of simple clinical scores such as NSS and diabetic neuropathy examination (DNE) scores were found to be simple and useful tools for the diagnose peripheral neuropathy in-patients with diabetes. Moreover, in the same study a good correlation between VPT score with tuning fork, monofilament and ankle reflex was found suggesting that simple bed side tests are useful in clinical practice, even in those subjects in whom foot care practices are not followed [5].

- Using NSS and NDS in T2DM patients has been found to be a useful resource in evaluating diabetic sensorimotor polyneuropathy as an important bed side tool [6,7] (Annexure XI).

Avoid walking bare foot

- Sociocultural practices like bare foot walking indoors and other religious places is one of the significant contributor of diabetic foot complications in India [8,9]. Additionally, use of inappropriate foot wear, injury while performing foot care practices were also found to be equally contributing to the development of foot complications [10]. Therefore the panel emphasized on educating patients on problems associated with walking bare foot [11] and advice on the use of appropriate/therapeutic footwear, particularly those at high-risk patients to prevent the development of foot deformities and ulceration [12].
- In a questionnaire-based study evaluating the foot care knowledge and practices with foot complications in 300 Indian patients suggests that majority of these patients were not educated previously about foot care and walked without foot wear indoors. The study emphasized that poor knowledge of foot care and poor footwear practices were important risk factors for foot problems in diabetes and called for a joint effort from doctors and footwear industry and to educate patients about foot care and improve their choice and selection of footwear so as to reduce foot problems [13].

Pressure off loading

- Pressure modulation commonly referred to as 'offloading' is an important component in the management and treatment of diabetic foot ulcers. It involves mitigation of pressure at an area of high vertical or shear stress [14]. Combining an effective, easy to use offloading devices such as total contact casts and removable cast walkers ensures patient compliance while heal foot ulcers and avert limb amputations [1,15].
- Mandakini off-loading device [16] and Samadhan offloading system [17] were found to be most economical, easy to apply and effective method to re-distribute the pressure in ulcerative areas.

Implementation

The availability of basic equipment, appropriate protocols, structured records and recall systems need to be supported by appropriate training for professionals providing screening and management services. Liaison needs to be established with orthoptists, footwear suppliers and cast technicians.

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Infections and vaccinations

RSSDI 2015 recommendations

Recommended care

- All adults' diabetes subjects should be educated about administering pneumococcal and influenza vaccine and those above the age of 60 years should be advised to be vaccinated
- Children with diabetes <2 years of age can be given pneumococcal polysaccharide vaccine and children above 6 months of age, influenza vaccine
- Other vaccines may be administered in patients with diabetes based on need
- Irrespective of age, immunization is recommended in all patients with:
  - renal failure
  - diabetes and immune-compromised state due to concomitant conditions
  - diabetes and chronic lung diseases like chronic obstructive pulmonary disease (COPD), bronchial asthma
  - diabetes patients who smoke
  - poor hygienic conditions (especially slum dwellers) and those who frequently travel to high risk areas
- Vaccination is contraindicated/postponed in patients with:
  - hypersensitivity to the active substances or to any of the excipients of the vaccine
  - history of chicken egg allergy particularly when considering flu shot
  - recent history of Guillain–Barre syndrome within 6 weeks of a previous influenza vaccination in the case of flu shot
  - post-poned in patients with febrile illness or any acute infection
- In patients with chicken egg allergy, chemoprophylaxis with amantadine/rimantadine or immunization using a protocol as reported by Murphy and Strunk may be considered

Limited care

- The principles for infections and vaccinations during diabetes are as for Recommended care subject to availability and affordability of pneumococcal and influenza vaccines

Preamble

The risk of developing infectious diseases due to diabetes is now being considered an important complication of diabetes [1]. Diabetes increases the risk of infection by 2 to 3 times in comparison to the non-diabetic population. The morbidity and mortality associated with infectious diseases such as influenza, pneumonia and hepatitis, which are usually preventable by appropriate vaccination, also appears to be very high in diabetes subjects [2]. Longer duration of diabetes and poor glycemic control causes increased risk of pneumonia related hospitalizations in diabetes subjects due to compromised immune system of the host [3]. A recent study demonstrated that patients with pre-existing diabetes are at increased risk of community-acquired pneumonia [4]. Even certain viral Infections can lead to new onset of diabetes in the population who are genetically prone to develop diabetes.

Considerations

The decision about conducting a screening program should be based on local factors such as limited resources and high prevalence of diabetes related infections factors that were reviewed in Indian context.

Rationale and evidence

Infections in diabetes

- Several factors have been implicated for the infections in diabetes, of which, altered immunity is the most predominant one [5]. Other predisposing factors increasing susceptibility to infections include diabetes related complications, frequent catheterization and dialysis in chronic renal failure patients. Evidence that these immunological defects can be corrected through good glycemic control support the importance of close monitoring of infectious diseases in subjects with diabetes [6].
- Urinary tract, respiratory tract, foot and deep soft infections are most common in diabetes mellitus occurring with increased incidence and resulting in high mortality [7].
- Following section deals with evidences from Indian and global studies on infections that commonly occur in patients with diabetes
  - Evidence that influenza can trigger coronary complications, when taken in the context of diabetic subjects, gains more significance since the risk for CVD is already 2- to 4-fold higher in this sub group [8].
  - Retroviral infections: Cirrhosis liver in diabetic patients results in higher incidence of glucose intolerance (60-96%) and overt diabetes (20-60%). Similarly in HIV patients undergoing active retroviral therapy, autoimmune diabetes may be caused due to protein inhibitors and nucleoside analogues. Therefore in patients with compensated cirrhosis, high insulin resistance and inflicted with HIV, insulin should be the preferred choice of treatment [9].
  - In diabetic population, Hepatitis B and C produces more comorbidities and prolonged infections.
  - Malignant otitis externa: Particularly occurs in patients with diabetes older than 35 years and is almost always due to pseudomonas aeruginosa. It can be prevented by creating proper awareness regarding healthy ear cleaning practices like, not using commercially available ear buds and other foreign objects or unsterilized cotton.
  - Infection of hand and upper limb: Diabetes ulcers in the upper limb should be promptly treated with adequate surgical drainage in order to prevent spread of infection. Creating awareness on healthy cleaning practices minimizes the disability and result in better outcome [10].
  - Urinary tract infections (UTIs): These mostly asymptomatic bacterial infections occurring more frequently in female diabetic patients. In all hospitalized diabetic patients it is recommended to perform urine culture to detect presence of bacteriuria ASB, a condition leading to an unexplained worsening of the glycemic control in some patients [11].
  - Hepatitis: It has been observed that in several patients with underlying diabetes, suffer from, prolonged or complicated course of acute viral hepatitis. It is possible that with impaired hepatocyte regenerating capacity, these patients run a more prolonged and complicated course.

- Infection due to Hepatitis B virus (HBV) may occur during monitoring of blood glucose and other procedures involving multi-patient use of finger stick devices designed for single-patient use and inadequate disinfection and cleaning of blood glucose monitors between patients [12].
- When Hepatitis C occurs in diabetic patients, the chronicity as well as risk of infections further increases.
- Hepatitis A is the most common vaccine-preventable virus acquired during travel and most common in the Indian subcontinent. Protection is proven to last at least 15 years [8].
  - Tuberculosis: Because diabetes impairs host defense mechanism, it has long been known to be a risk factor for active tuberculosis (TB) and reactivation of latent TB [13]. Evidence suggests that the risk of developing TB is increased among patients with diabetes, particularly during the first year after diagnosis of diabetes [14]. Furthermore it is associated with worse treatment outcomes, higher rates of relapse and higher mortality rates in patients affected by both diseases. The situation is particularly challenging in low-income and middle-income countries where TB is endemic. Data from a systematic review of 13 observational studies indicate that efforts to diagnose, detect, and treat diabetes early may have a beneficial impact on TB control [15].

Types of vaccines

- Various types of vaccinations recommended to prevent these infections are [16,17]:
  - Pneumococcal vaccination:

- Pneumococcal polysaccharide vaccine (PCV7 and PCV13)
- Pneumococcal conjugate vaccine (PPV)
  - Influenza vaccination
  - Hepatitis B vaccination

– Hepatitis A vaccination

- Annexure XII provides a brief information on recommended vaccines for patients with diabetes.

Methods to improve rate of vaccination

- Maintaining a diabetes registry, systemic tracking system, and reminder system serve as tools for improvising the acceptance to vaccination and communicating with the subjects for the need of vaccination which provides awareness on immunization [18].
- Periodic training of the staff accompanied by ongoing assessment of immunization rates and work flow and also a close follow up with the vaccine or his care giver by the treatment team which is beneficial in minimizing the risk of inappropriate re-vaccinations [19].
- The protocols should also aim at implementing a quality assurance process so that the standards of care are maintained [17].

Implementation

Apart from the micro and macro vascular events in diabetes, infections due to influenza and pneumococci should be considered a significant public health concern. All the clinics using vaccinations shall maintain the records to assess the efficacy of vaccines regarding occurrence of various complications in vaccinated compared to non-vaccinated and vaccination strategies in diabetes should evolve as part of routine care and a central registry need to be maintained.

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Fasting and diabetes

RSSDI 2015 recommendations

Recommended care

- Fasting is not recommended and is best avoided in persons with T2DM especially if they also have:
  - uncontrolled or unstable glycemic values
  - history of recurrent diabetic ketoacidosis, inter-current illness
  - significant macrovascular complications
  - significant microvascular complications
  - history of hypoglycemic unawareness (elderly)
- T2DM patients should abstain from fasting if:
  - On intensive insulin therapy
  - non-adherent (in terms of following advice on diet, drug regimens, and daily activities)
  - experiencing frequent hypoglycemic episodes (hypoglycemia without any symptoms)
  - antenatal or nursing
- Persons with diabetes who wish to fast must consult a physician prior to fasting and should be encouraged to participate in pre fast counselling/assessment to optimize monitoring/therapeutic strategies for optimal glycemic control
- During fasting, persons with diabetes should always:
  - carry some sweets/other source of glucose to use in case of hypoglycemia
  - carry identification card displaying diabetic status and current medication
  - test blood glucose levels regularly (also, if unwell during fasting)
  - treat promptly if glucose levels are deranged
  - end the fast immediately if dehydrated or hypoglycemic
  - speak to the physician regarding change in dose, timing and time of insulin injections
- Patients with diabetes should be educated to increase the awareness on risks of fasting
- Newer sulfonylureas – sustained release gliclazide/ glimepiride, incretin based therapies – sitagliptin/ vildagliptin and liraglutide if one can afford and pioglitazone are preferred agents to be used during Ramadan or other fasts spread over a number of days or weeks

Limited care

- The principles for management of diabetes during fasting are as for Recommended care

Preamble

Religious fasting is a means of inculcating discipline in an individual but not to impose excessive hardship [1]. Fasting is a time of great spiritual growth and can also improve physical well-being if properly undertaken. Though preference for religious fasting is a personal decision, persons with diabetes may fast after careful risk assessment and counselling with healthcare professionals and religious leaders, who help the individual make an informed decision [2]. Fasting may have different connotations in different religions. It does not necessarily mean abstaining from food. For example, in the Jain religion, many eat the last meal before sunset and is considered a form of prayer. Similarly in Ramadan, one who cannot fast can feed the needy to offer prayer. Depending on the degree of abstinence from food, fasts may be classified as follows:

Type of fast
• Complete fasting: giving up food and water completely for a period
• Partial fasting: eating less than you need to avoid hunger
○ Limiting the number of items of food eaten
○ Giving up favorite foods

However it should be noted that almost all the religions provide special concessions to believers who are ill, travelling or unable to keep fasts due to some reason or the other.

Considerations

Factors that may influence glucose lowering therapy/strategy during fasting is based on the following factors:

Fasting	Glucose lowering therapy	Individual phenotype
• Duration of fast • Restriction of fluids/ solids: absolute/partial • Frequency of fast (once weekly/ once monthly/ once yearly/ others)	• Potential for hypoglycemia • Potential for dehydration • Potential for gastrointestinal upset • Duration of action	• Risk of hypoglycemia • Risk of hypoglycemia unawareness • Ability to self-monitor blood glucose

Rationale and Evidence

Pre fast counselling/assessment

- Discussion about fasting should be initiated prior to the fast. This should include the potential discomforts and risks of fasting, and means of mitigating them. The person's exact perspective of fasting, including duration of fast, allowance for liquids and snacks during the day, acceptance of sublingual foods, and freedom to break the fast in case of significant discomfort must be clarified [3].
- Pre fast assessment, comprises comprehensive history taking, physical examination, and investigations aimed at identifying stigmata of target organ damage, so that strategies can be made to optimize health during fasts [4]. Pre fast counselling should include hypoglycemia awareness training.
- Factors that may increase the risk of hypoglycemia, hypoglycemia unawareness, and dehydration must be noted [5]. The concept of shared decision making and person centeredness must be followed, in letter and inspirit while considering whether a particular individual can fast safely or not [6].
- SMBG should be considered as an important tool that helps both patients and physicians to practice safe decision making regarding drug dosage and other aspects of management [7]. Evidence suggests that among patients with T2DM, increase in frequency of SMBG was associated with better glycemic control in those who were on insulin, and were able to adjust their regimen [8].

Religious fasts

Though several guidelines are available for different aspects of diabetes care, fasting in diabetes poses a unique challenge [1,9]. Designing randomized controlled trails to address the issues related to fasting in patients with diabetes is particularly difficult. Therefore, understanding the physiology of fasting and linking it to pathophysiology and clinical manifestation of diabetes is required to design strategies for glycemic management during fasting [10]. We summarize different religious fasts commonly observed in India that can have significant impact on metabolic and glycemic health in diabetes:

- Ramadan fasting: It is a principle ritual followed by Muslims during the sacred month of Ramadan (the ninth lunar month of Islamic/Hijri calendar) [9]. During this month all healthy adult Muslims abstain from food, drinks and medication from dawn to dusk (sunset). Believers usually eat two times, one before dawn (Suhur) and one after sunset (Iftar). Hypoglycemia and dehydration are major complications associated with fasting, though hyperglycemia may occur, due to over indulgence in food during the two main meals of Suhur and Iftar [11]. Therefore pre fast risk stratification, followed by a treatment tailored to individual needs appears to be best management strategy. In addition, structured education enables patients to self-manage their condition better [12].
- Jain fasts: There are two sects in the Jain religion, the Shwetambers and the Digambers. The fasts are similar in both sects, except for the duration of fasting during the pious month of Paryushana eight days for the Shwetamber sect, and ten days for the Digamber sect. Jains usually fast from dusk to dawn, unlike Hindu fasting which extend from dawn to moon-rise [3].
- Hindu fasts: Though not mandatory, most of the Hindus observe day-long and week-long fasts. Karva Chauth, Guru Purnima, Ekadashi, Makar Sakranti and Hoi Ashtami are some of the annual, monthly and weekly fasts observed as part of various vows. During Navratras, which occur twice a year, Hindus observe longer fasts for a period of 9 days usually from dawn to moon-rise/star-rise. The day-long nature of Hindu fasts however makes it distinct from the month-long fasts of Ramadan and Buddhist Lent. Unlike in Islam, there are no universal rules laid down for Hindu fasts, and therefore data on metabolic effect of these fasts is scanty so far [3].

Pharmacological management

- Newer generation sulfonylureas (gliclazide MR and glimepiride) should be preferred over older, long acting sulfonylureas like glibenclamide and chlorpropamide during Ramadan fasting as they are relatively more safe and economical [1].
- Pioglitazone was found to safe and efficacious in lowering blood glucose in fasting subjects during Ramadan in combination with other OHAs [13].
- Agents that can act on incretin system may maintain adequate glycemic control in a glucose-dependent manner, thus providing a safe alternative therapeutic option during Ramadan [10]:
  - Vildagliptin was found to be effective, safe, and well tolerated in T2DM patients fasting during Ramadan, with a consistently low incidence of hypoglycemia across studies, accompanied by good glycemic and weight control [14].
  - Switching anti-hyperglycemic treatment to sitagliptin from a SU reduced the risk of symptomatic hypoglycemia by approximately 50% in patients who fasted during Ramadan [15].
  - In Treat 4 Ramadan trial, liraglutide compared with sulphonylurea was well tolerated with more patients

achieving target HbA1c, lose or maintain weight with no severe hypoglycemia and with high level of treatment satisfaction. This suggests that liraglutide may be considered an effective therapy in combination with metformin during Ramadan [16].

- SGLT-2 inhibitors may be used during fasting, in view of their low risk of hypoglycemia. However, the potential risk of dehydration must be taken into account.
- Use of a rapid acting insulin analogue instead of regular human insulin before meals in patients with T2DM who fast during Ramadan was associated with less hypoglycemia and less post prandial glucose excursions [17].
- Detailed information on categories of risk in patients with T2DM who fast during Ramadan can be found in Annexure XI.
- Detailed information on recommended changes in treatment regimens of oral antidiabetic agents and insulin in patients with T2DM who fast during Ramadan and other religious fasts can be found from references 11 and 17.

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Conflict of interest

All the authors including SV Madhu, Banshi Saboo, Brij Mohan Makkar, Gundam Chandrasekhara Reddy, Jayaprakashsai Jana, Jayant K Panda, Jitendra Singh, Narasimha Setty, Paturi V Rao, Rajeev Chawla, Rakesh Kumar Sahay, Samar Banerjee, Sarita Bajaj, SR Aravind, Vasant Kumar and Vijay Paniker have no conflict of interest to declare.

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Annexures

Screening/early detection of diabetes/prediabetes

Annexure I

The indian diabetes risk score (IDRS)

- The tool encompasses four parameters: age, abdominal obesity, family history of diabetes, and physical activity to detect T2DM and also helps to distinguish T2DM from non-T2DM.
- A maximum score of 100 is given for these categories combined as shown in the figure.
  - Subjects with an IDRS of <30 are categorized under low risk, 30-50 as medium risk and those with > 60 as high risk for diabetes.
  - Similarly waist circumference ≥90 cm, sedentary lifestyle and family history of diabetes are indicators for high risk of diabetes.
  - Limiting the blood sugar testing to those with an IDRS score of 50 and above could identify more than 90% of Indians with diabetes and prediabetes.

Parameter	Score
Age	
<35 years	0
35-49 years	20
≥50 years	30
Waist circumference	
Waist <80 cm (female), <90 cm (male)	0
Waist ≥80-89 cm (female), ≥90-99 cm (male)	10
Waist ≥90 cm (female), ≥100 cm (male)	20
Physical activity	
Regular vigorous exercise or strenuous (manual) activity at home/work	0
Regular moderate exercise or moderate physical activity at home/work	10
Regular mild exercise or mild physical activity at home/work	20
No exercise and/or sedentary activities at home/work	30
Family history of diabetes	
No diabetes in parents	0
One parent is diabetic	10
Both parents are diabetic	20

Minimum score=0; Maximum score=100; Positive score≥60/100

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Diet therapy

Annexure II

General recommendations for diet in diabetes patients

- When blood glucose is under control, 100 gms of fruit(e.g. Papaya, sweet lime, orange, guava etc.) should be allowed daily
- Whole fruits are recommended rather than fruit juices
- At least one vegetable dish has to be included in the daily menu.
- Roots and tubers can be consumed once a week by diabetic patients, but should be included as calorie-suppliers
- Low calorie foods like tea, coffee, skimmed milk (without sugar), buttermilk, salads etc. are allowed for diabetic patients.
- Cream from milk should be removed before consuming

GI: glycemic index

Reference

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Annexure III

Diet in diabetes patients with established CVD

Highly recommended	Moderately recommended	Not recommended
Leafy vegetables, vegetable salads, coarse grains, sprouted grams, spices and all other foods which are rich in fiber and antioxidants	Low fat milk and milk products, vegetable oils with MUFA and PUFA, flesh foods (fish, chicken without skin, white of the egg) and artificial sweeteners	Alcohol, sugar, saturated fats and foods that are refined, processed, salt-rich, cholesterol- rich and deep-fried

CVD: cardiovascular disease; MUFA: mono-unsaturated fatty acids, PUFA: polyunsaturated fatty acids

Reference

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Lifestyle management

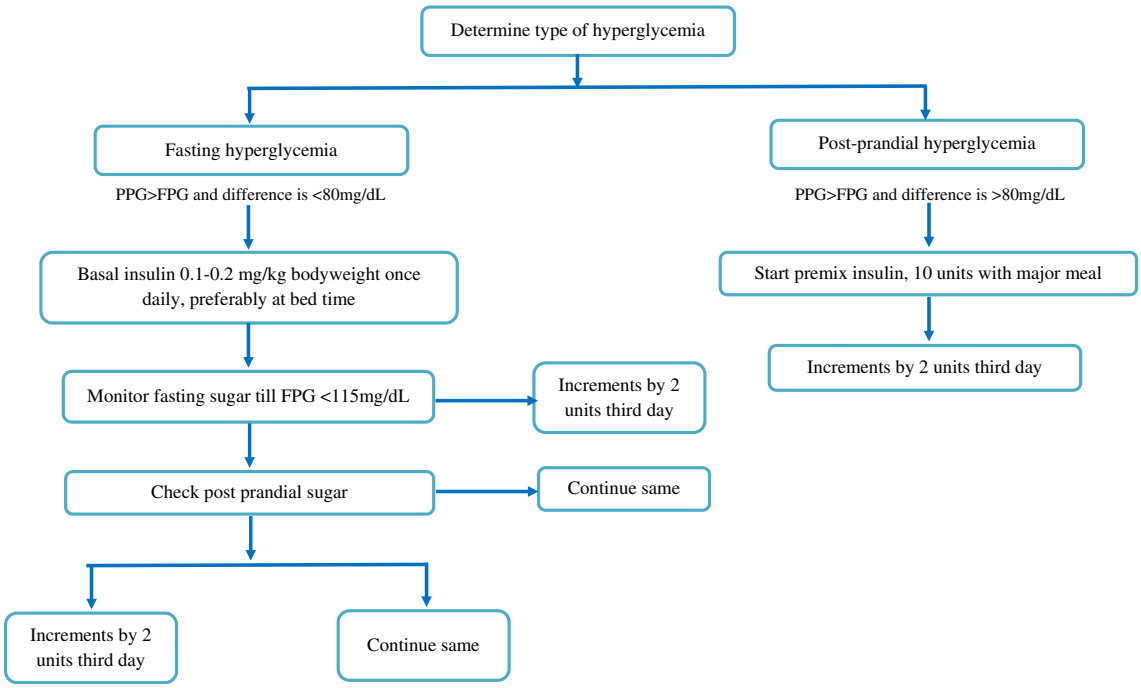
Annexure IV

General guidelines: exercise therapy in diabetes

- Patients with diabetes should exercise as part of their medical management
  - Exercise used to reduce weight should be combined with dietary measures
  - Moderate intensity aerobic activity and resistance training should be a part of the exercise regimen
- Multiple short exercise sessions lasting at least10 min each in course of a day are useful
- Exercise should be appropriate to the persons general physical condition and life style
- Use proper foot wear and If appropriate, protective equipment
- Avoid exercise in extreme hot or cold
- Inspect feet before and after exercise

Insulin therapy

Annexure V
Approaches for initiating insulin



Annexure VI

Steps for initiation of basal therapy

	Glucose value	Total Daily Dose
Step 1. Initiationwith basal insulin*	HbA1c <8%	0.1-0.2 units/Kg
	HbA1c >8%	0.2-0.3 units/Kg
Step 2. Titration# (every 2-3 days to reach glycemic goals)	Fixed regimen	Increase by 2 units/day
	Adjustable regimen	
	FPG >180 mg/dL	Add 4 units
	FPG 140-180 mg/dL	Add 2 units
	FPG 110-139 mg/dL	Add 1 unit
Step 3. Monitor for hypoglycemia	BG< 70 mg/dL	Reduce by 10 to 20%
	BG< 40 mg/dL	Reduce by 20 to 40%

Abbreviations: HbA1c: glycated hemoglobin; BG: Blood Glucose; FPG: Fasting plasma glucose; NPH: Neutral Protamine Hagedorn; SU: Sulfonylureas

*consider discontinuing SU therapy and basal analogues should be preferred over NPH insulin

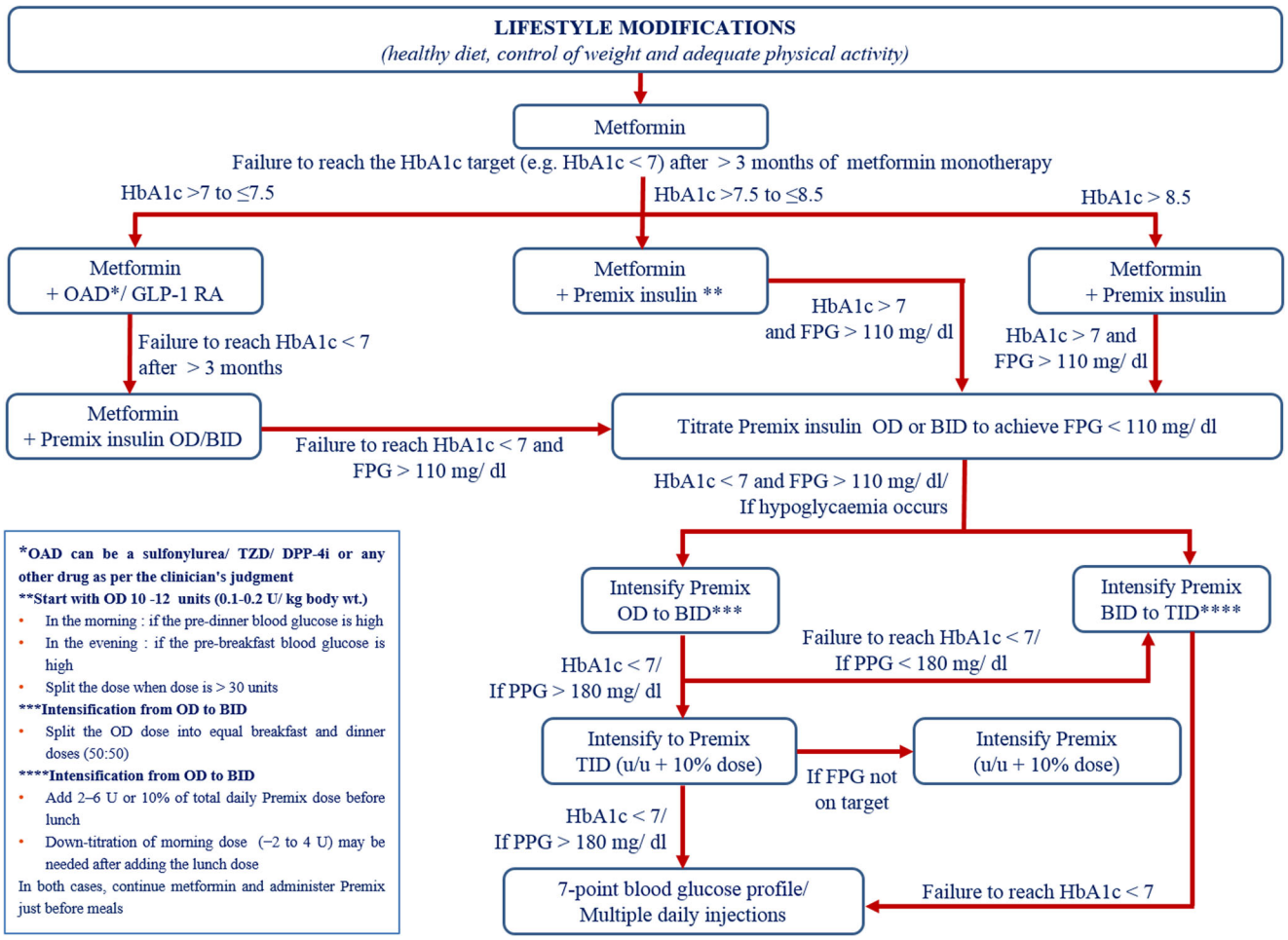
For most patients with T2D taking insulin, glucose goals are HbA1c<7% and fasting and premeal blood glucose <110 mg/dL in the absence of hypoglycemia. HbA1c and FPG targets may be adjusted based on patients age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

Adapted from

1. Handelsman Y, Bloomgarden ZT, Grunberger G, Umpierrez G, Zimmerman RS, Bailey TS, et al. American association of clinical endocrinologists and american college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. Endocr Pract. 2015;21 Suppl 1:1-87.

Annexure VII

Steps for initiating premixed Insulin



Annexure VIII

Steps for intensification of insulin therapy

	Therapeutic option	Total Daily Dose
Step 1. Add prandial insulin	When glycemic targets are unmet	TDD 0.3-0.5 units/kg (50% basal: 50% prandial)*
Step 2. Titration# (every 2-3 days to reach glycemic goals)	Fixed regimen (Prandial insulin)	Increase TDD by 2 units/day
	Adjustable regimen (Prandial insulin)	
	FPG >180 mg/dL	Increase TDD by 4 units
	FPG 140-180 mg/dL	Increase TDD by 2 units
	FPG 110-139 mg/dL	Increase TDD by 1unit
	2-h PPG or next premeal glucose > 180 mg/dL	Increase prandial dose for the next meal by 10%
	Premixed Insulin	
	FPG/Premeal BG > 180 mg/dL	Increase TDD by 10%
Step 3. Monitor for hypoglycemia	Fasting hypoglycemia	Reduce basal insulin dose
	Night time hypoglycemia	Reduce basal insulin or reduce short/rapid-acting insulin taken before supper or evening snack
	Between meal hypoglycemia	Reduce previous premeal short/ rapid acting insulin

Abbreviations: BG: blood glucose; DPP-4: dipeptidyl peptidase 4 inhibitors; FPG: fasting plasma glucose; GLP-1: glucagon-like peptide 1 receptor agonists; NPH: neutral protamine Hagedorn; PPG: postprandial glucose; SGLT-2: sodium glucose cotransporter 2; TDD: total daily dose.

*Basal + prandial insulin analogs preferred over NPH+ regular insulin or premixed insulin. #For most patients with T2D taking insulin, glucose goals are HbA1c <7% and fasting and premeal blood glucose <110 mg/dL in the absence of hypoglycemia. HbA1c and FPG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk.

Adapted from

1. Handelsman Y, Bloomgarden ZT, Grunberger G, Umpierrez G, Zimmerman RS, Bailey TS, et al. American association of clinical endocrinologists and american college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. Endocr Pract. 2015;21 Suppl 1:1-87.

Chronic complications: diabetic nueropathy

Annexure IX

Diabetic neuropathy symptom score (NSS) (Meijer et al. 2002)

NSS Questionnaire

1. Are you suffering of unsteadiness in walking? Need for visual control, increase in the dark, walk like a drunken man, lack of contact with floor.
2. Do you have a burning, aching pain or tenderness at your legs or feet? Occurring at rest or at night, not related to exercise, exclude intermittent claudication.
3. Do you have prickling sensations at your legs and feet? Occurring at rest or at night, distal>proximal, stocking glove distribution.
4. Do you have places of numbness on your legs or feet? Distal>proximal, stocking glove distribution

The questions were answered either 'Yes' (positive: 1 point) if symptom has occurred during the last 2 weeks or 'No' (negative: no point) if it did not. Maximum score is 4 and minimum 0.

Annexure X

Modified neuropathy disability score (Boulton. 2005)

Neuropathy Disability Score (NDS)

		Right	Left
Vibration Perception Threshold 128-Hz tuning fork; apex of big toe: normal = can distinguish vibrating/not vibrating	Normal = 0 Abnormal = 1		
Temperature Perception on Dorsum of the Foot Use tuning fork with beaker of ice/ warm water			
Pin-Prick Apply pin proximal to big toe nail just enough to deform the skin: trial pair = sharp blunt: normal = can distinguish sharp/not sharp			
Achilles Reflex	Present = 0 Present with reinforcement = 1 Absent= 2		
	NDS Total out of 10		

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Diabetic foot care

Annexure XI

Diabetic neuropathy examination

Muscle strength
1. Quadriceps femoris: extension of the knee
2. Tibialis anterior: dorsiflexion of the foot
Reflex
3. Triceps surae
Sensation: index finger
4. Sensitivity to pinpricks
5. Monofilament and vibration perception threshold
Sensation: big toe
6. Sensitivity to pinpricks
7. Sensitivity to touch
8. Vibration perception
9. Sensitivity to joint position

Only the right leg and foot are tested.
Scoring from 0 to 2:
0 = Normal
1 = Mild/moderate deficit
• Muscle strength: medical research council scale 3–4
• Reflex: decreased but present
• Sensation: decreased but present
2 = Severely disturbed/absent
• Muscle strength: medical research council scale 0–2
• Reflex: absent
• Sensation: absent
Maximum score: 16 points

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Infection and vaccinations

Annexure XII

Recommended vaccines for diabetic patients

Vaccines	Dosage
Pneumococcal (polysaccharide)	1 or 2 doses
Influenza	1 dose TIV annually
Tetanus diphtheria Pertussis (Td/Tdap)	• Substitute 1- time dose of Tdap; then boost with Td every 10 years
Measles mumps rubella(MMR)	• 1 or 2 doses, 4 week interval
Varicella	• 2 doses, at least 4 weeks apart
Zoster	• 1 dose, 60 yrs.
Hepatitis A	• 2 doses at least 6 months apart.
Hepatitis B	• 3 doses
Human papillomavirus (HPV) Female	• 3 doses through age 26 years. • The second dose should be administered 1–2 months after the • first dose • Third dose should be administered 6 months after the first dose (at least 24 weeks after the first dose).
Human papillomavirus (HPV) Male	• 3 doses through age 21 years

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Annexure XIII

Categories of risk in patients with T1DM or T2DM who fast during Ramadan

Category	Medical advice
Very high risk • Severe hypoglycemia within the last 3 months prior to Ramadan • Patient with a history of recurrent hypoglycemia • Patients with hypoglycemia unawareness • Patients with sustained poor glycemic control • Ketoacidosis within the last 3 months prior to Ramadan • Type 1 diabetes • Acute illness • Hyperosmolar hyperglycemic coma within the previous 3 months • Patients who perform intense physical labor • Pregnancy • Patients on chronic dialysis	Should NOT fast, has high probability of harm
High risk • Patients with moderate hyperglycemia (average BG between 150 and 300 mg/dL, HbA1c7.5–9.0%) • Patients with renal insufficiency • Patients with advanced macrovascular complications	Should NOT fast, has high probability of harm

• People living alone that are treated with insulin or sulfonylureas	
• Patients living alone	
• Patients with comorbid conditions that present additional risk factors	
• Old age with ill health	
• Drugs that may affect mentation	
Moderate risk	Should fast, low probability of harm
• Well-controlled patients treated with short-acting insulin secretagogues such as repaglinide or nateglinide	
Low risk	Should fast, low probability of harm
• Well-controlled patients treated with diet alone, metformin, or a thiazolidinedione who are otherwise healthy	

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